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# The American Heart Journal

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## Original Communications

### CHANGES IN HEART VOLUME IN ADDISON'S DISEASE AND THEIR SIGNIFICANCE

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THE fact that the hearts of patients who die of Addison's disease are unusually small has attracted considerable attention.<sup>1, 2, 3</sup> On the other hand, there has been little or no comment upon the variations in the size of the heart which occur during life in any of the several stages of adrenal insufficiency. With the discovery and perfection of potent therapeutic agents, these changes should assume more than academic interest. Cardiac dilatation and pulmonary congestion have already been reported in two patients who were undergoing treatment with large doses of adrenocortical hormone.<sup>4</sup> The rapid retention of sodium and water in such patients may be but part of the explanation for the cardiac embarrassment.

The present observations suggest that chronic insufficiency of the adrenal cortex produces a diminution in the size of the heart which is directly related to a loss of cortical function. The further, sudden decrease which occurs when crisis supervenes appears to be the result of lowered blood volume, and disappears when dehydration is corrected.

#### METHODS AND MATERIALS

Six patients with Addison's disease formed the basis of the study.

Cardiac volume was estimated from the frontal and sagittal cardiac silhouettes according to the method of Rohrer<sup>5</sup> and Kahlstorf,<sup>6</sup> as modified by Comeau and White,<sup>7</sup> except that teleroentgenography was employed instead of orthodiasecopy, and measurement of the frontal cardiac area was made by means of accurately ruled graph paper which contained subdivisions of 0.04 sq. cm. It is obvious that any method of calculating heart volume in vivo is faulty, not only because the heart fails to correspond accurately to any geometric figure, but also because the normal variations consequent upon body build are considerable.<sup>8</sup> The present observations are of comparative value in so far as multiple estimations in each of a series of patients are concerned.

Surface area was estimated by means of Boothby and Sandiford's nomogram.<sup>9</sup>

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Blood volume was calculated by an adaptation of the Congo red method of Rowntree, Brown, and Roth.<sup>2</sup> While the factors of error, as suggested by Gibson and Evans,<sup>10</sup> make for inaccuracy in absolute values, all conditions of the estimations were standardized. The readings are therefore believed to be reliable for comparative purposes in the case of any one patient. Normal standards for blood volume were derived from the graph of Gibson and Evans,<sup>10</sup> which relates them to height (ht) or surface area (Sa), and from the tables of Rowntree, et al.,<sup>2</sup> which add a factor for "fullness index."

Serum sodium was estimated by the method of Hawk and Bergeim,<sup>11</sup> and serum potassium by that of Kramer and Tisdall as modified by Rappaport.<sup>12</sup> The daily intake of sodium and fluid was only approximated but is believed to be accurate within  $\pm 5$  per cent.

Potent commercial extracts of adrenal cortex and synthetic adrenocortical hormone\* were used throughout the study, as indicated.

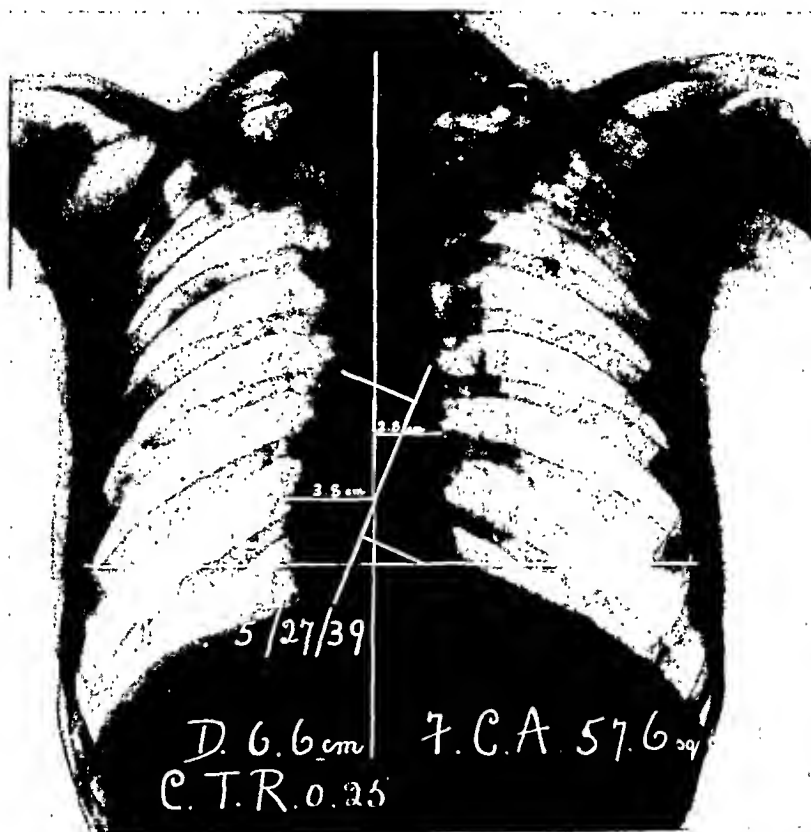


Fig. 1a.

Fig. 1.—Case 1: Roentgenograms of chest (a) during a crisis; (b) during period of cortical insufficiency, but after recovery from crisis; (c) when fully stabilized on synthetic cortical hormone. Note striking changes in size of the frontal cardiac area.

#### CASE REPORTS

CASE 1.—K. K., a 36-year-old Greek, whose illness had begun 1.5 years prior to admission to the hospital with anorexia, alternating periods of diarrhea and constipation, asthenia, pigmentation of the skin, and the loss of approximately 45 pounds of weight, for one month prior to admission had been bedridden as a result of weakness and entered the hospital in a crisis.

\*Desoxycorticosterone acetate in oily suspension for injection, and sterile compressed tablets for subcutaneous implantation were furnished by Dr. Max Gilbert, of the Schering Corporation, whose courtesy is herewith gratefully acknowledged.

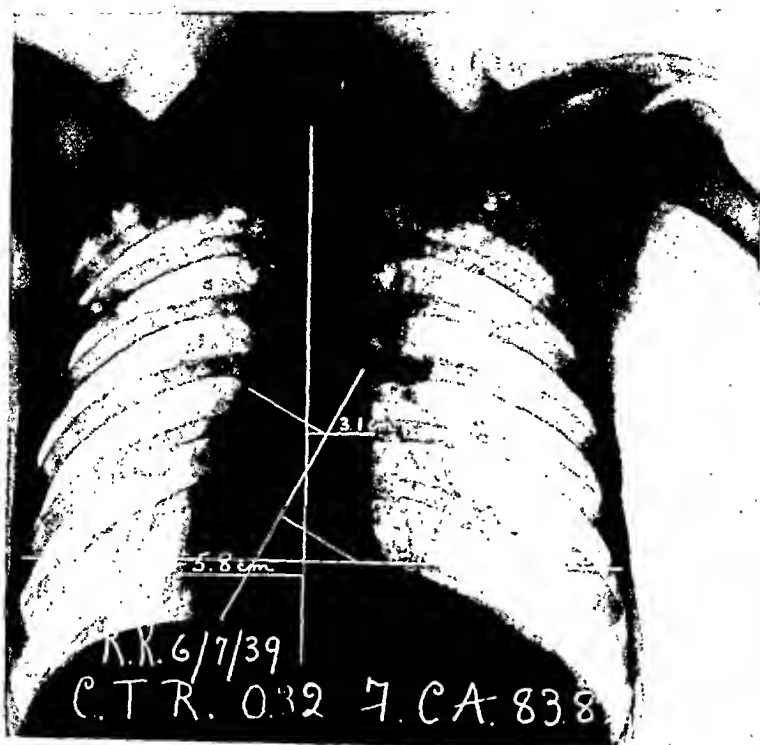


Fig. 1b.

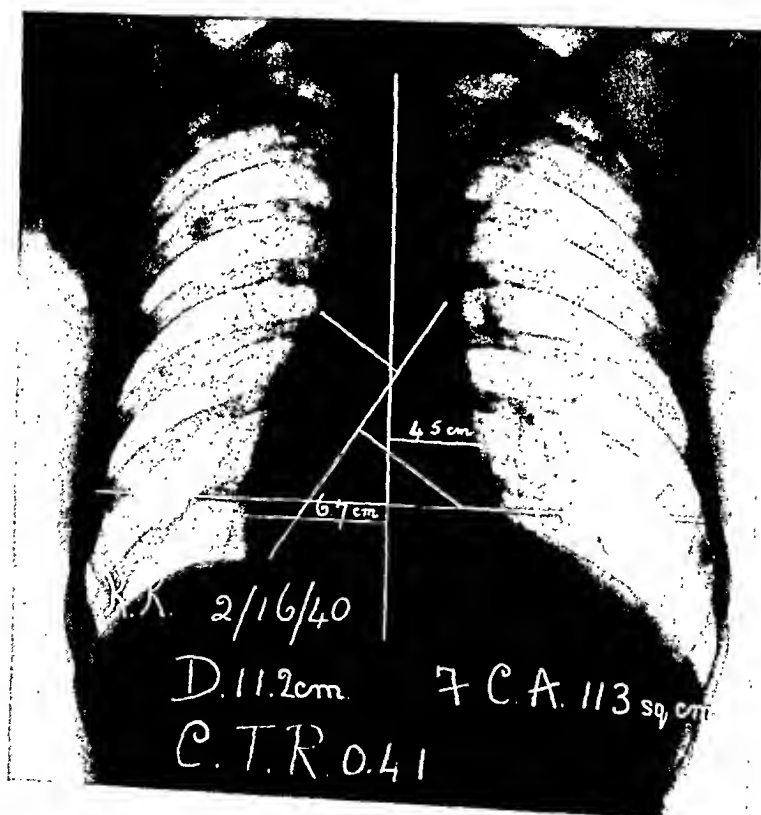


Fig. 1c.

He was a cold, drowsy, lethargic, well-developed, but emaciated, man who was 161 cm. tall and weighed 40 kg. There was deep, generalized pigmentation of the skin. Discrete areas of similar pigmentation were present on the buccal mucous membrane. The tongue was normal. At the apices of both lungs, bronchovesicular breathing and fine subcrepitant râles were heard. The cardiac borders were made out with difficulty; the heart sounds were distant and of poor quality. The blood pressure was 80/50.

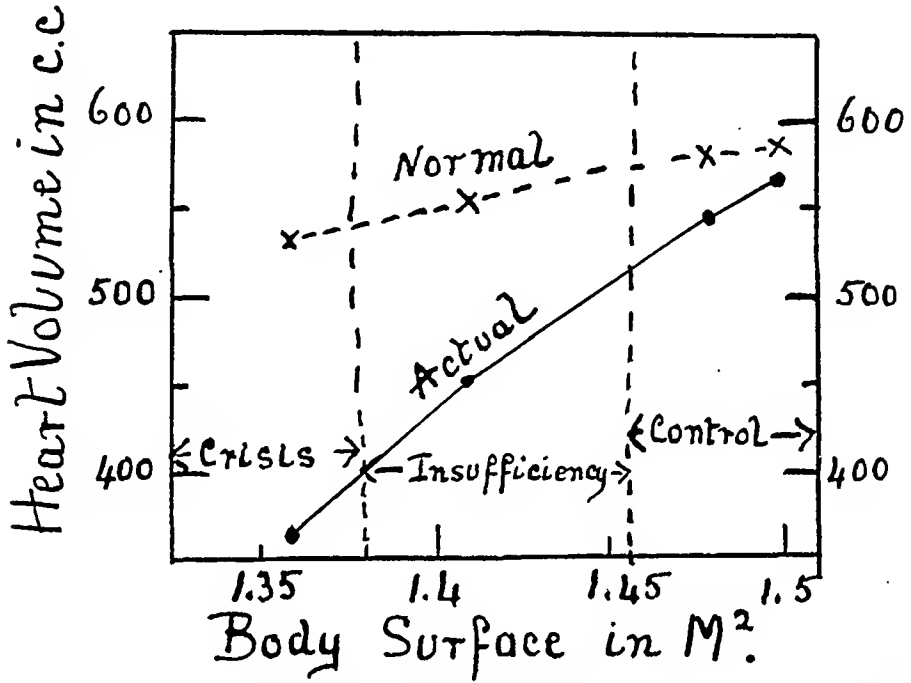


Chart I.—Relation of heart volume to body surface in various stages of Addison's disease (Case 1).

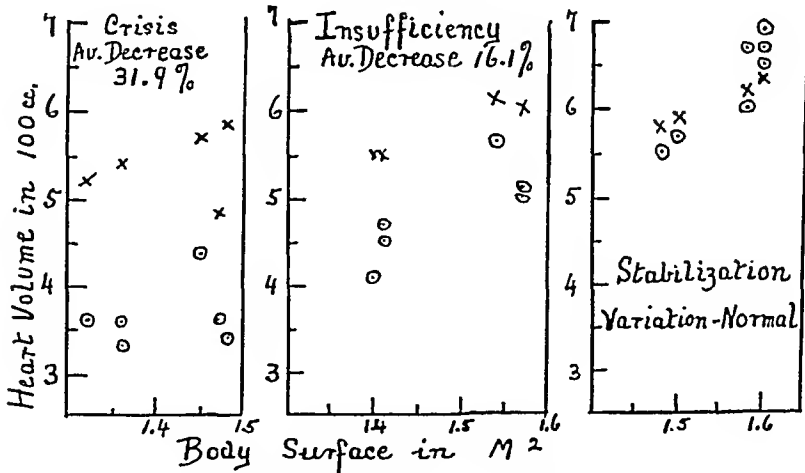


Chart II.—Relation of heart volume to body surface in various stages of Addison's disease. (X = Theoretic values. O = Actual values.)

Laboratory data (Table I) on admission. The urine showed a specific gravity of 1.018, a faint trace of albumin, many hyaline and granular casts, and an occasional, cuboidal, epithelial cell, but no blood or pus. The erythrocyte count was 4,360,000 per c.mm., the hemoglobin, 89 per cent, and the leucocyte count, 14,900 per c.mm.; the differential count showed, in per cent, polymorphonuclear cells, 67; eosinophiles, 3; lymphocytes, 28; and monocytes, 2. The total blood volume was 2,903 c.c. The

TABLE I  
RELATION OF HEART SIZE, BLOOD VOLUME, BLOOD PRESSURE, AND ELECTROLYTE BALANCE IN VARIOUS STAGES OF ADDISON'S DISEASE  
AGE 36 YEARS

CASE 1													
HEIGHT 161 CM.													
DAY OF OBS.	WT. (KG.)	B.P.	C.T.R. <sup>a</sup>	F.C.A. <sup>b</sup>	HEART VOL. PER KG.	HEART VOL. C.C./M <sup>2</sup>	TOTAL BLOOD VOL. (C.C.)		SERUM IN MG. %		DAILY INTAKES <sup>d</sup>		CLIN. CONDITION <sup>e</sup>
							ACTUAL	THEORETIC <sup>c</sup>	Na	K	Na (GM.)	HORMONE <sup>e</sup>	
I	40	80/50	0.25		7.1	208.1	2903	4268	260.0	25.3	11.0	10 (E)	C.
11	41.8	96/50	0.32		9.9	296.2	4320	4501	265.5	10.3	K2.0	4 days	
30	42.7	104/70	0.38		9.2	277.4	4200	4517	279.0		11.0	5 (E)	C. I.
51	40.0	74/50	0.26	74.2	9.3	263.6		4268	259.0		No treatment three weeks		C. I.
58	42.3	90/60	0.34	92.4	10.7	322.0			292.0		11.0	0	I. C.
112	47.7	120/80	0.42	110.6	11.5	371.9		4755	341.0	14.0	K2.0	5 (S)	C. I.
154	50.0	140/80	0.39	101.8	10.2	337.8		4797	382.0	13.4	K2.0	5 (S)	F. S.
256	50.0	130/82	0.41	113.0	11.4	379.7	4730	4797	355.0	17.8	K2.0	5 (S)	F. S.
											6.0	300 (I)	F. S.

(a) C.T.R., Cardiothoracic ratio

(b) F.C.A., Frontal cardiac area

(a) C.T.R., Cardiothoracic ratio

(b) F.C.A., Frontal cardiac area

(c) Rowntree, et al.<sup>2</sup>

(d) Represents daily intake or dose begun on date noted and continued to time of next observation.

(e) Glandular extracts (E) in c.c.

Synthetic hormone in mg.—oily suspension for injection (S)

—compressed tablet for implant (I)

(f) C, Crisis; I.C., impending crisis; C.I., cortical insufficiency; F.S., fully stabilized.

carbon dioxide combining power of the blood plasma was 52 volumes per cent. The values for the blood chemical constituents, in milligrams per cent, were: (for the plasma) nonprotein nitrogen, 54.3; urea nitrogen, 28.7; creatinine, 2.1; inorganic phosphorus, 7.2; sugar, 69.0; and sugar after the ingestion of 100 Gm. of glucose (readings at half-hour intervals), 92, 98, 106, 88, 65, 65; and, for the serum, chlorides (as NaCl), 429; sodium, 260; and potassium, 25.3. The basal metabolic rate was plus 0.5 per cent. Roentgenographie examination revealed a tuberculous infiltration in the infraclavicular regions of both lungs, more extensive on the left side. The heart was very small. Small, calcified areas were seen just above the right kidney, in the region of the adrenal gland. The electrocardiogram showed a low  $T_1$  and a biphasic  $T_2$  and  $T_3$ , with notching of the T in both chest leads.

The course of this patient can be followed by referring to Table I. The symptoms and signs of crisis were relieved within four days. On the eleventh hospital day the blood cell counts and nonprotein nitrogen content of the plasma were normal and remained so thereafter. The patient's clinical improvement paralleled the changes in weight, blood pressure, serum sodium, and so forth, as seen in Table I. Glucose tolerance curves on the thirtieth, the fifty-eighth, the one hundred twelfth, and the two hundred fifty-sixth days of observation varied little from the initial one; there was a high tolerance in every instance.

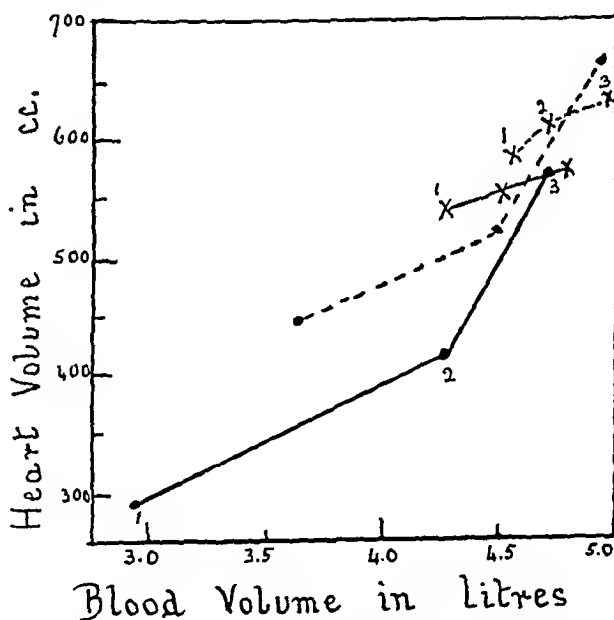


Chart III.—Relationship of heart volume to blood volume in Addison's disease as compared with the normal. (— = Case 1. - - - - = Case 2. ● = Actual values. X = Theoretic "normal" values.)

At the present time, with subcutaneous implants of desoxycorticosterone totaling 300 mg., he is able to do half-time work without loss of weight or strength. The changes in heart volume and their relation to body surface, to blood volume, to various stages of the disease, and to the normal, are shown in Table I, Charts I, II, and III, and in Fig. 1.

CASE 2.—G. V., a 24-year-old white Italian, was admitted to the hospital because of bilateral, caseous, pneumonic tuberculosis, with a large cavity in the right upper lobe. His infection had begun two years previously with a right-sided pleurisy. At the time of admission he was a well-developed man with signs of disease in the apices of both lungs. The heart was normal in size, shape, and position; the heart

TABLE II  
RELATION OF HEART SIZE, BLOOD VOLUME, BLOOD PRESSURE, AND ELECTROLYTE BALANCE IN VARIOUS STAGES OF ADDISON'S DISEASE  
AGE 24 YEARS

CASE 2													
				HEIGHT 153 CM.									
DAY OF OBS.	WT. (KG.)	B.P.	C.T.R. <sup>a</sup>	F.C.A. <sup>b</sup>	HEART VOL. PER KG.	HEART VOL. C.C./M <sup>2</sup>	TOTAL BLOOD VOL. (C.C.)		SERUM IN MG. %		DAILY INTAKE <sup>d</sup>		CLIN. CONDITION <sup>e</sup>
							ACTUAL	THEORETIC <sup>c</sup>	Na	K	Na (GM.)	HORMONE <sup>f</sup>	
1	58.4	115/80	0.41	98.6	11.5	424.7							
152	60.2	118/80	0.39	88.0	9.9	378.9						Ward diet	
195	59.8	96/66	0.36	95.0	10.5	402.8						Ward diet	
239	58.0	88/70	0.34	85.8	9.8	368.5	4520	4776	308.0	22.4	11.5	0	C. I.
291	50.0	78/50	0.31	72.5	9.2	321.3	3680	4555	290.0	31.7	15.0	0	C. I. I. C.

Symbols (see Table 1).

Symbols (see Table I).



rate was 85; the blood pressure was 115/80; the cardiac mechanism was normal; the pulmonic second sound was accentuated; and no murmurs were heard.

Among the laboratory data were an erythrocyte count of 3,550,000, a hemoglobin value of 80 per cent, and a leucocyte count of 11,600, with a normal differential count. The urine was normal. The sputum gave a Gaffkey 4 reaction for tubercle bacilli. The blood sugar was 110 mg. per cent, and the total nonprotein nitrogen, 33.7 mg. per cent.

The patient's condition improved slightly during the first 150 days of hospitalization. He gained two kilograms in weight, and there was some clearing of the lesions in the apices. On the one hundred ninety-fifth day of observation his blood pressure had dropped to 96/66, and there was a questionable change in skin coloration, but no alteration in the volume of the heart could be detected (Table II). Thereafter, he grew steadily worse. On the two hundred thirty-ninth day he had all of the manifestations of adrenal cortical insufficiency (Table II), with a diminution in heart volume, a serum potassium of 22.7 mg. per cent, and a serum sodium of 308.0 mg. per cent, but his blood volume was normal (4,520 c.c.). Forty-five days later he had a crisis, with still further lowering of his blood pressure (78/50), blood sodium, and cardiac volume, an elevation of serum potassium to 31.7 mg. per cent, and a total blood volume of only 3,680 c.c. (Table II). He died of adrenal cortical insufficiency on the three hundred sixteenth day of observation.

CASE 3.—E. M. was a 53-year-old, well-developed and well-nourished German woman. She had had a cholecystotomy because of cholelithiasis at the age of 38, a cholecystectomy because of cholelithiasis at the age of 50, scanty, irregular menses, and had passed the menopause at the age of 48. She had first noticed pigmentation of the skin three years previously. During the preceding six months this had become progressively worse and had been associated with loss of weight (approximately 20 pounds), gradually increasing anorexia, asthenia, abdominal pain, vomiting, and diarrhea.

The most remarkable thing about the patient was a generalized pigmentation of the entire body, the tongue, and the buccal mucous membrane. The fingernails and toenails showed a very deep purplish-black color which varied considerably in intensity from day to day. The heart sounds were of poor quality. The blood pressure was 96/60. She weighed 58.2 kg. and was 145 cm. tall.

Repeated urinalyses were negative; there was no hematoporphyrinuria, hemoglobinuria, hemosiderinuria, or urobilinuria. The icteric index was 6. There was a mild secondary anemia. The basal metabolic rate was plus 6. The Mantoux reaction was positive. The serum proteins were normal. The values for the other blood chemical constituents, in milligrams per cent, were: nonprotein nitrogen, 28.0; urea nitrogen, 11; creatinine, 1.4; sugar, 88; serum sodium, 276; serum potassium, 20; serum chlorides (as NaCl), 410; calcium, 10; inorganic phosphorus, 3.75; cholesterol, 125; cholesterol esters, 52.5. These remained approximately the same on repeated examinations, with the exception of the sodium, potassium, and chloride values, which, three days prior to death, on the seventy-fifth day, were 367, 8.7, and 562, respectively.

The electrocardiogram and roentgenograms of the lungs, abdomen, and skull were essentially normal. The heart was small. Its transverse diameter was 10.4 cm.; the cardiothoracic ratio was 0.42; and the heart volume was 228 c.c. per square meter of body surface.

The patient was given approximately 12 Gm. of sodium and 10 to 40 c.c. of adrenal cortical extract daily. Temporary improvement followed, but after two weeks on a diet which contained approximately normal amounts of sodium a sudden relapse occurred, and the patient died in twenty-four hours, despite the administration of 18 Gm. of sodium and 50 c.c. of cortical extract.

*Autopsy.*—The heart weighed 195 Gm. The left adrenal was small, atrophic, and flat; it weighed 2 Gm. The right adrenal was almost completely destroyed by a hemorrhage which had been caused by thrombosis of the artery.

CASE 4.—N. R., a 41-year-old, asthenic, emaciated, white woman, had been losing weight gradually for one year; she had also had weakness, cutaneous pigmentation, and nausea, of increasing degree. For five days prior to admission she had been confined to bed, because of weakness, nausea, and diarrhea. When she was admitted, she was in shock, was mildly disoriented, and was "too weak to raise her head." There was a brownish pigmentation of the skin of the hands and face, and, to a less marked degree, of that of the trunk. The heart was small and the sounds distant. The blood pressure was 76/40. She weighed approximately 45.4 kg. and was 163 cm. tall.

The urinalysis was negative. There was hemoconcentration, with a moderate leucocytosis. The nonprotein nitrogen content of the blood was 46 mg. per cent, and the serum sodium was 240.1 mg. per cent. Roentgenograms of the chest revealed inactive, bilateral apical tuberculosis and a small heart. The transverse diameter of the heart was 7.4 cm.; the cardiothoracic ratio was 0.30; and the heart volume was 245 c.c. per square meter of body surface.

Improvement followed a high intake of sodium (15 Gm. daily) and fluid (3,500 c.c. daily). On the third day the patient's family took her home, and attempts to follow her course have failed.

CASE 5.—W. P., a 46-year-old, emaciated, white woman, was admitted to the hospital in a state of shock, with a history that her illness had begun with seasickness six months previously. Nausea, weakness, anorexia, diarrhea, and dyspnea had appeared in the order named. Physical examination revealed circumscribed areas of pigmentation over the entire body and the buccal mucous membrane. The heart sounds were feeble, but there were no murmurs. The blood pressure was 120/60. Three days later her weight was 38.6 kg., and her height, 157 cm. The erythrocyte count was 4,800,000; the hemoglobin, 97 per cent; and the leucocyte count, 12,600. The serum sodium was 266 mg. per cent. The transverse diameter of the heart was 9.5 cm.; the cardiothoracic ratio, 0.39; and the cardiac volume, 271.9 c.c. per kilogram of body weight. The electrocardiogram showed a high normal P-R interval (0.20 sec.), small and slightly slurred QRS complexes, and low T waves in all leads. As a result of the daily administration of 2,000 to 3,500 c.c. of fluid, 15 Gm. of sodium, and 10 to 30 c.c. of cortical extract parenterally, the patient's condition was markedly improved, and she was discharged on the thirty-fifth day.

CASE 6.—E. M., a 42-year-old, emaciated Irishman, who was admitted to the hospital during an impending crisis, had developed, over a period of two years, weakness, pigmentation of the hands, face, and genitalia, loss of weight, and attacks of nausea and vomiting, all of which were steadily increasing in severity. On admission he complained of upper abdominal pain which was so severe as to suggest the presence of an acute surgical condition.

He weighed 52.7 kg., was 165 cm. tall, and showed irregular pigmentation of the entire body surface, but no mucous membrane lesions. His lungs appeared to be normal; the heart was small; and the blood pressure was 66/55. The upper abdomen was tender and slightly rigid; the temperature was subnormal. The urine was negative except for a trace of albumin. The erythrocyte count was 5,000,000; the hemoglobin, 100 per cent; and the leucocyte count, 19,200, with a normal differential count. The values for the blood chemical constituents, in milligrams per cent, were: (for the plasma) nonprotein nitrogen, 46; sugar, 91; and sugar after the ingestion of 100 Gm. of glucose (readings at half-hour intervals), 91, 92, 115, 82, 73, 80; and (for the serum) sodium, 288; potassium, 25.9; and chlorides (as NaCl), 420. A frac-

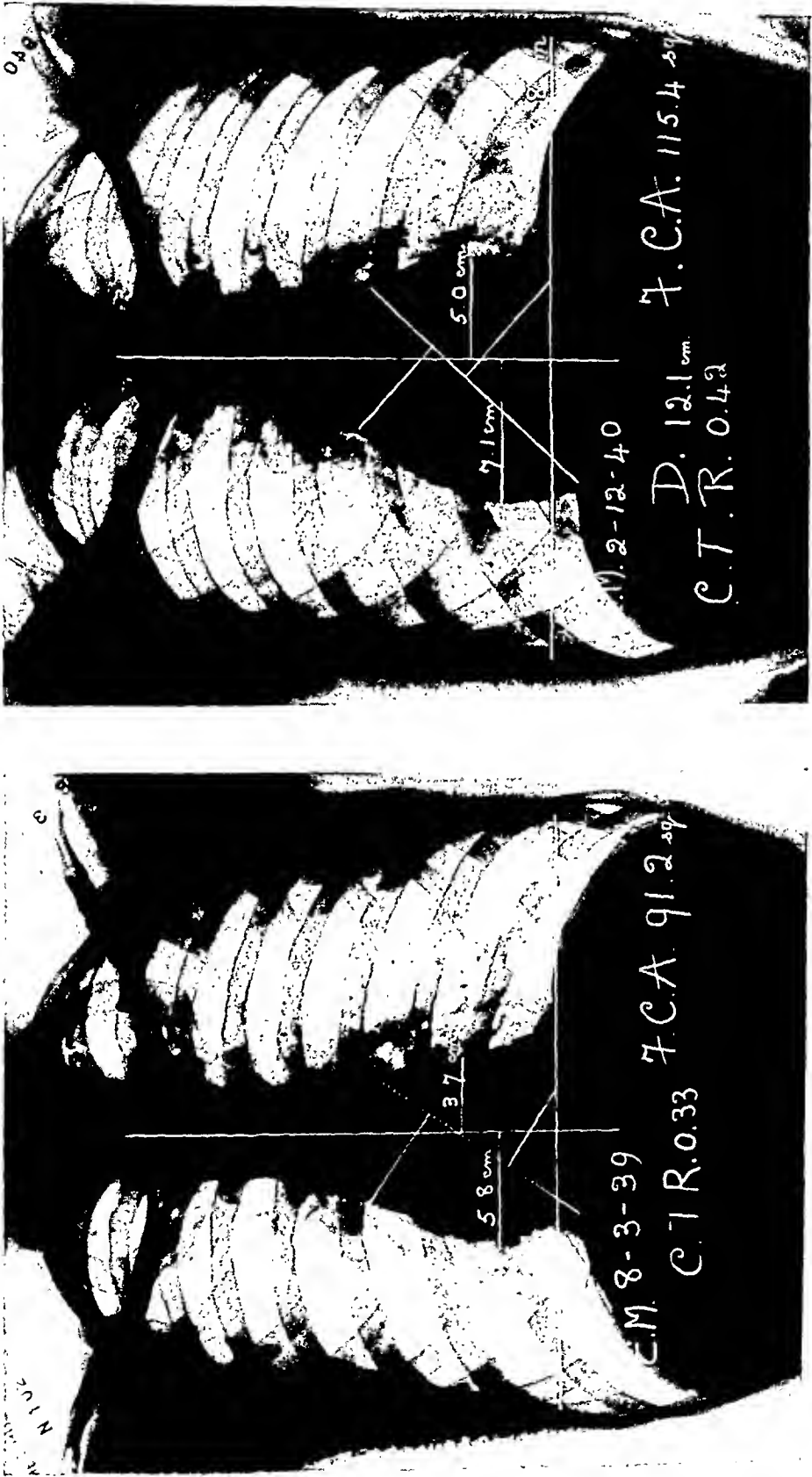


Fig. 2a.

Fig. 2b.

Fig. 2.—Case 6: Roentgenograms of chest (a) during cortical insufficiency; (b) after full stabilization on desoxycorticosterone.

TABLE III  
RELATION OF HEART SIZE, BLOOD VOLUME, BLOOD PRESSURE, AND ELECTROLYTE BALANCE IN VARIOUS STAGES OF ADDISON'S DISEASE

AGE 42 YEARS		CASE 6										HEIGHT 165 CM.	
DAY OF OBS.	WGT. (KG.)	B.P.	C.T.R. <sup>a</sup>	F.C.A. <sup>b</sup>	HEART VOL. PER KG.	HEART VOL. C.C./M <sup>2</sup>	TOTAL BLOOD VOL. (C.C.)		SERUM IN MG. %		DAILY INTAKE <sup>d</sup>		CLIN. CONDITION <sup>e</sup>
							ACTUAL	THEORETIC <sup>c</sup>	Na	K	Na (GM.)	HORMONE <sup>e</sup>	
2	52.7	66/55	0.33	91.6	9.8	330.8			288.0	25.9	12.0	2.5 (E)	I. C.
9	52.7	80/50	0.33	91.2	9.8	329.3			275.7		12.0	10 (E)	I. C.
36	53.1	95/75	0.45	118.8	11.0	372.6			350.0	25.1	12.0	10 (S)	C. I.
55	53.6	130/70	0.46	110.4	12.0	413.8			448.0	12.4	6.0	7.5 (S)	F. S.
143	55.4	140/90	0.46	118.8	12.8	444.3			314.0	13.9	6.0	5.0 (S)	F. S.
198	53.8	124/80	0.42	115.4	12.8	437.0			308.0	20.2	6.0	5.0 (S)	F. S.

Symbols\* (see Table I).

tional gastric analysis showed nothing abnormal. The basal metabolic rate was minus 10 per cent. Roentgenologic examination disclosed discrete, calcified, healed, tuberculous foci in the apices of both lungs. The heart shadow was small; its transverse diameter was 9.3 cm. The cardiothoracic ratio was 0.33; and the heart volume was 330 c.c. per square meter of body surface (Fig. 2). In all leads of the electrocardiogram there were slurring of the R wave and low amplitude of the T waves. Subsequent blood cell counts and glucose tolerance curves showed little change. When the patient was fully stabilized, the plasma volume was 3,692 c.c. and the total blood volume was 4,995 c.c.

The patient was given 12.0 Gm. of sodium and 10 to 30 c.c. of adrenal cortical extract daily. His subsequent course can best be followed by referring to Table III and Fig. 2. The size of the heart increased slowly during the first four weeks but was not restored to normal until the patient was given desoxycorticosterone acetate (7.5 mg. daily). On the one hundred seventeenth day of observation two tablets of desoxycorticosterone, each weighing 150 mg., were implanted subcutaneously. Thereafter it was possible to discontinue all injections, except for a short febrile period when supplemental injections of 5 mg. of the drug, in oil, were given daily.

#### DISCUSSION

The transverse diameter of the heart was below normal limits in each patient who showed signs of cortical insufficiency and was most strikingly altered during crises. In contrast to the "horizontal depth diameter," which varied but little from time to time in any individual patient, the transverse measurement underwent wide fluctuations which roughly paralleled the severity of the Addison's disease.

The cardiothoracic ratio, that is, the transverse diameter of the heart divided by the transverse diameter of the thorax, afforded an even more accurate index of the seriousness of the disease.

With the exception of Case 3, the measurements in which were made when a crisis was impending, a cardiothoracic ratio below 0.40 invariably represented cortical insufficiency, and ratios below 0.32 occurred only during crises. When adequate treatment for the adrenal deficiency was instituted, as, for instance, in Cases 1 and 6, the ratios ranged from 0.41 to 0.46. The estimation of cardiothoracic ratios from serial tele-roentgenograms suggests itself as a logical method of following the effects of therapy in Addison's disease, except in cases in which the chest is unusually flat or deep, as noted by Liljestrand, et al.<sup>13</sup> Our Case 3 was an instance of this type of thorax; the patient had a normal cardiothoracic ratio but a markedly reduced heart volume per kilogram of body weight (5.8 c.c.).

In any individual chest, however, cardiac volume is a reasonably constant function of the "frontal cardiac area." In no instance did the frontal cardiac area of a patient in crisis exceed 77.0 sq. cm., and in but one such instance was the cardiac volume per square meter of body surface above 300 c.c. (302.4 c.c.) The difficulty which is encountered in obtaining absolute values for the volume of the heart in the living subject has already been stressed.<sup>7</sup> It has been found that there is a linear correlation between heart volume and body weight or body surface.

Comeau and White,<sup>7</sup> after a study of 170 normal persons, state that "this correlation, however, was not sufficiently close to allow the derivation of a reliable index as a criterion for normal." The same problem is inherent in the work of Liljestrand, et al.,<sup>12</sup> who, however, estimated an average mean heart volume for each of two groups of men whom they studied. This mean figure has been used for the determination of the theoretically normal heart volume in our charts. Although we recognize the fallacies of such a method, the differences in the various stages of adrenal insufficiency seem to be so marked as to offer little room for controversy. From examination of Charts I and II, it is clear that heart volume is disproportionately reduced in relation to surface area in patients with adrenal insufficiency. In five cases, during crises, the average reduction amounted to 31.9 per cent (Chart II), whereas it was 16.1 per cent in three persons with adrenal insufficiency who were not having crises. The heart volume was normal in Patient 2 before the development of Addison's disease, and attained normal proportions in Patients 1 and 6 after adequate hormonal therapy.

The relation of these changes in heart volume to alterations in total blood volume in Cases 1 and 2 is shown in Chart III. Significant blood volume changes seem to occur only during crises and are the result of sodium and water loss from the body. These alterations, chiefly, if not wholly, in the plasma and tissues,<sup>14</sup> account for a definite portion, but not for all, of the variations in heart volume that we observe in Addison's disease. Blood volume can be restored to normal by the administration of sufficiently large quantities of water and salt, but heart volume returns to normal only when adequate amounts of adrenocortical hormone are also supplied (Chart III). This would suggest that the adrenal cortex has a definite effect upon heart size, a fact which is borne out by studies of autopsy material.<sup>1, 15</sup> Moreover, recent experimental work on rats<sup>16</sup> has shown that thymic hyperplasia and splenomegaly follow adrenalectomy, whereas thymic atrophy and splenomegaly are produced by the administration of either the adrenotropic hormone of the pituitary or adrenocortical hormone.

It may be contended by some that this disproportionate decrease in heart size is the result of simple inanition, or "starvation." However, in guinea pigs, prolonged starvation has little effect upon "the normal heart weight/body weight ratio."<sup>17</sup> Again, the weights of the atrophic hearts of rats which were suffering from thirst, starvation, and vitamin B deficiency showed the same ratio to body weight as the heart weights of normal animals of the same size.<sup>18</sup> Lusk<sup>19</sup> quotes Voit's very early observations on the starved cat, which confirm the above observations and even suggest that the decrease in cardiac weight may be disproportionately small. Finally, Smith,<sup>20</sup> in a study upon human beings, states that "there is a definite correlation between the weight of the heart and the weight of the body. . . . The ratio is slightly higher in thin persons."

Estimations of heart volume may eventually prove to be of value in calculating optimum dosage of adrenocortical hormones. Until recently, overdosage was virtually impossible, for sufficiently potent materials were not available. With the advent of synthetic material, notably desoxyeorticosterone, and the prospect of obtaining an extract of the cortex itself which is believed to be 100 times as effective as the present synthetic material,<sup>21</sup> the possibility of overdosage has become real.<sup>4</sup> Ferrebee and his associates<sup>4</sup> noted edema of varying degree in ten of thirteen patients treated. Three patients developed respiratory distress, with roentgenologic evidence of pulmonary congestion, and in two of them serious cardiac insufficiency, with dilatation, was observed. Following prompt therapy one recovered, but the other died of a complicating pneumonia. We have not seen these complications, but our dosages of hormone have not been as large as those originally used by the above-mentioned workers. In an addendum to their communication, they state that this complication can be avoided by using smaller doses of hormone and not giving more than the usual amount of salt in the diet.

In Cases 1, 3, and 6, it will be noted that high sodium values were maintained in the blood during periods of stabilization as long as the sodium intake was held at a high level (approximately 12.0 Gm. daily). These diminished promptly in Cases 1 and 6 when a general ward diet, containing approximately 6.0 Gm. of sodium, was resumed. It was thought at first that the point of hormonal tolerance could be determined by blood sodium levels and glucose tolerance tests. The experiences mentioned above, and those of Ferrebee and his associates,<sup>4</sup> have shown the dangers which are inherent in using sodium estimations as a sole criterion of optimal dosage. Glucose tolerance curves were influenced but little by the synthetic hormone (Cases 1 and 6) in doses which, nevertheless, appeared to contain ample amounts of the "vital factor." Wells and Kendall<sup>22</sup> found that retention of sodium and a depression of potassium to low levels resulted from the use of desoxyeorticosterone and its acetate. The depression of potassium was evident in all of our cases, but the rise of sodium to high levels occurred only under desoxyeorticosterone treatment when the intake of sodium was concomitantly high, viz., 12 or more Gm. daily. Is it possible that the cortical hormone is even more complex than was suggested by the work of Hartman and his associates,<sup>23</sup> who succeeded in separating a "vital" and a "sodium regulating" fraction? Inasmuch as blood sodium values may be readily influenced by salt ingestion, and blood glucose levels remain low despite therapy, it may be profitable to turn to a study of teleroentgenograms, together with blood pressure and weight changes, as safe methods for ascertaining the optimal procedure in the management of the patient with Addison's disease. When transverse cardiac diameter, cardiothoracic ratio, and heart volume have been

restored to normal the dosage should be curtailed to a point at which a general sense of well-being is maintained, and a gradual gain in weight and strength is attained.

#### SUMMARY

1. In six cases of Addison's disease the relationship between cardiac mensuration and the stage of the disease was studied.

2. An average reduction in heart volume of 31.9 per cent was observed in five instances of crisis, and of 16.1 per cent in three patients with cortical insufficiency who were not having crises.

3. Prior to the development of Addison's disease, one patient had a cardiac volume which was within normal limits. Two others who were first observed during a crisis, and with a crisis impending, respectively, regained a normal heart volume when they were adequately treated.

4. Serial estimations of blood volume were carried out upon two patients. Significant lowering was seen only during crises. Values within the normal range were noted in patients with cortical insufficiency who were not having crises.

#### CONCLUSION

The reduction in cardiac volume observed in Addison's disease is a direct effect of the inadequate supply of adrenocortical hormone. When crisis supervenes, the diminished blood volume plays a striking accessory role in still further decreasing the size of the heart.

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# THE USE OF THE CATHODE RAY FOR RECORDING HEART SOUNDS AND VIBRATIONS

## II. STUDIES ON THE MUSCULAR ELEMENT OF THE FIRST HEART SOUND

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OVER a period of many years a multitude of experiments have been focused on the cause of the heart sounds and on various cardiac and circulatory conditions that influence them. The work has been fraught with difficulties, one of the greatest of which obviously lay in experimentation on the heart itself. Many ingenious experiments were devised with the object of studying the movements of the heart valves and how those movements produce or influence the heart sounds. Other experimental work aimed at silencing the valves, so that, if sounds are produced by the contracting myocardium, they could be detected and studied. Another difficulty appears to have been with the recording instruments which were employed. The earlier devices for registering the heart sounds graphically were crude. In recent years many refinements have been made in these methods, and the introduction of electric stethographs has marked a distinct advance. Most of the stethographs, however, are so designed that they record only the higher frequencies of the audible normal or adventitious sounds, or fail to record vibrations of too low an intensity to be heard.<sup>1</sup> By these means, however, much valuable information has been obtained.

It is now generally believed that the second heart sound is produced by the closure of the aortic and pulmonary semilunar valves. The cause of the first heart sound, however, is still a moot question. The statement is commonly made in standard textbooks (as pointed out by Dock<sup>2</sup>) that the first heart sound is composed of muscular and valvular "elements", although usually there are no discussions as to the nature of those respective elements. Many workers have clung to the belief that muscular components are present in the first sound,<sup>3, 4, 5, 6</sup> but have emphasized the role of the auriculoventricular valves in producing and modifying it. More recently, Dock<sup>2</sup> was led to the conclusion that the contracting myocardium plays no part in the causation of the first heart sounds, and that closure and tensing of the auriculoventricular valve leaflets are entirely responsible for the audible vibrations during normal ventricular systole.

We have reinvestigated the problem, with the hope of throwing more light on the components of the first heart sound. In a preliminary report, a general outline of the work was presented.<sup>7</sup>

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## METHOD

These experiments depend upon the immobilization of the auriculoventricular valves in such a way that the myocardium is permitted some latitude of contraction, so that the vibrations produced by the heart muscle alone can be detected and studied. The experiments were accomplished by the following method:

In each case the dog was anesthetized with veterinary nembutal. The thorax was opened by a midsternal incision, and respiration was maintained by a respiratory pump. The superior and inferior venae cavae were isolated (the azygos vein was completely ligated), so that rubber-padded clamps could be applied to the vessels to prevent any flow of blood to the heart. Small balloons, affixed to brass tubes 3 mm. in diameter, were introduced into the ventricular cavities by passing them through small incisions in the auricular appendages and pushing them through the auriculoventricular ostia. The balloons were so small when deflated that they did not interfere with cardiac function. The pericardium was left intact but was fastened to the diaphragm in order to prevent random movements of the heart; care was taken to avoid stretching the membrane and impairing normal cardiac movement. A few micrograms of barium chloride in saline were usually administered intravenously in order to decrease the likelihood of ventricular fibrillation as a result of the manipulation.

The heart sounds were recorded by means of a cathode-ray "vibrocardiograph." The instrument registers the wide range of vibrations produced by the heartbeat, some of which are of high enough frequency and intensity to comprise the heart sounds; the remainder are of low frequency and are not appreciated by the human ear. A description of the device and of the character of the cardiac vibrations registered by this method has been presented,<sup>1</sup> and need not be repeated here. In these experiments, the microphone of the vibrocardiograph was placed directly on the heart at the intraventricular septum, just above the apex. In order to prevent jarring of the microphone case, which would introduce artifacts into the curves, the instrument was suspended by rubber straps from a frame over the thorax, allowing the microphone button to rest firmly on the heart. The intact pericardium prevented friction between the receiver and the moving myocardium. Lead II of the electrocardiogram was obtained by embedding copper electrodes in the shoulder and thigh muscles. The paper speeds of the electrocardiograph and stethograph were matched, and the two records were synchronized by flashing lamps (flashing signals, occurring at intervals of 0.2 second) which played on the records simultaneously. A pair of crystal earphones which was connected to the amplifier of the stethograph permitted simultaneous auscultation of the heart. The latter auscultatory observations could be supplemented by placing the bell of an ordinary stethoscope on the ventricles.

The venae cavae were then clamped, and the "intraventricular" balloons carefully inflated with water or air to pressures of 50 to 70 mm. of mercury. These pressures distended the ventricles to approximately the normal diastolic size, and the balloons exerted sufficient pressure against the auriculoventricular valves to immobilize them and prevent change of tension in the valve membranes during systole. This was confirmed by experiments on hearts immediately after death, in which it was found that pressures of 50 mm. Hg in the balloons were more than adequate to render every part of the auriculoventricular valves quite inactive. The resilience of the balloons and the mobility of the manometric system permitted some degree of ventricular contraction against pressures more comparable to normal.

In addition, the experiments performed by Dock<sup>2</sup> were repeated. The heart vibrations were studied when the venae cavae were clamped and when the heart was contracting "isometrically." In the latter case, a ligature was passed around the auriculoventricular groove to prevent any blood flow to or from the ventricles. The

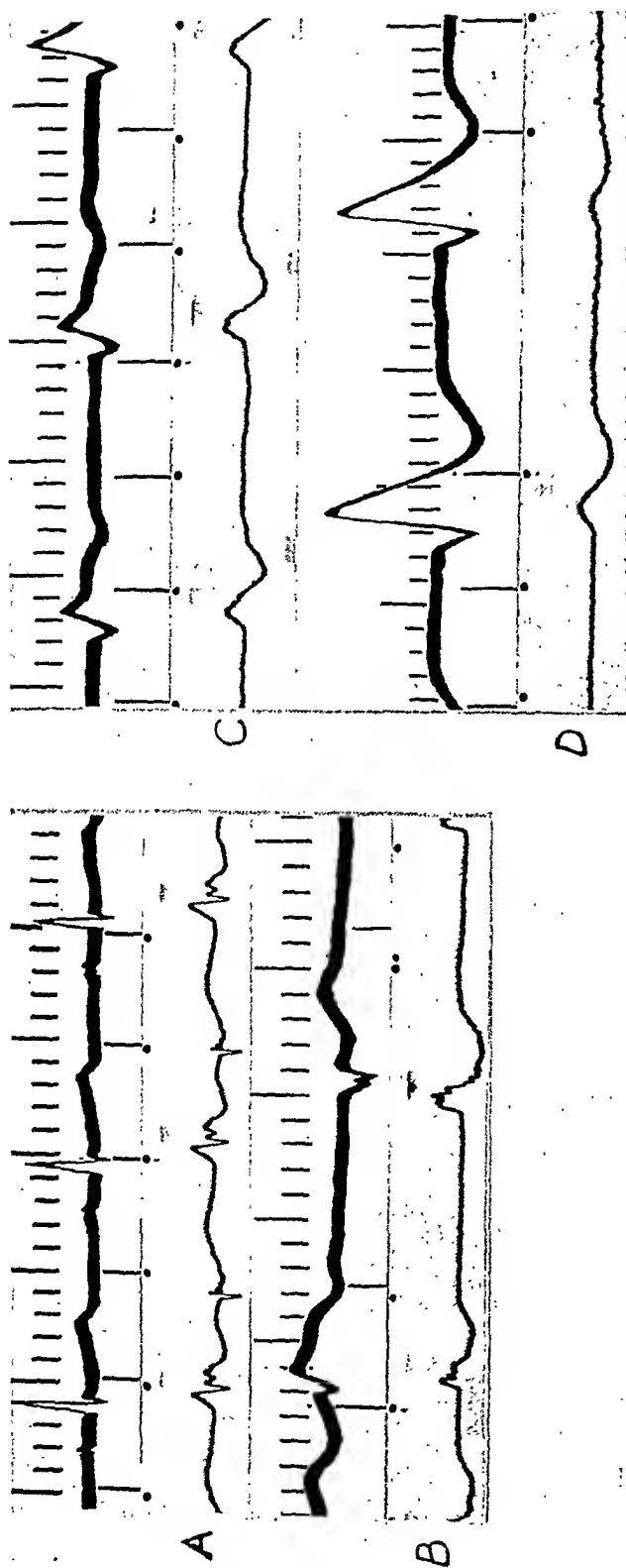


Fig. 1.—Electrocardiographic and vibrocardiographic curves obtained before and during inflation of balloons placed within the ventricular cavities (see text). The curves of the two instruments were synchronized by flashing lamps at intervals of 0.2 second. Since the paper speeds were not exactly the same, the flashing signals were occasionally interrupted, so that exactly synchronous points on each record could be determined, from which subsequent events in each could be measured. In this illustration, the electrocardiographic curve has been retouched to permit better reproduction.

normal functioning of the atrioventricular valves was abolished by the lack of intraventricular pressure change in the former instance, and by the cord about the A-V groove in the case of the "isometrically" contracting heart.

### RESULTS

Following clamping of the venae cavae and inflation of the intra-ventricular balloons, the first heart sound persisted until severe myocardial failure supervened. The train of events will best be understood by examination of the curves. Fig. 1 illustrates a typical experiment from this series. Fig. 1A is a control curve obtained with the microphone resting directly on the heart, before the venae cavae were clamped

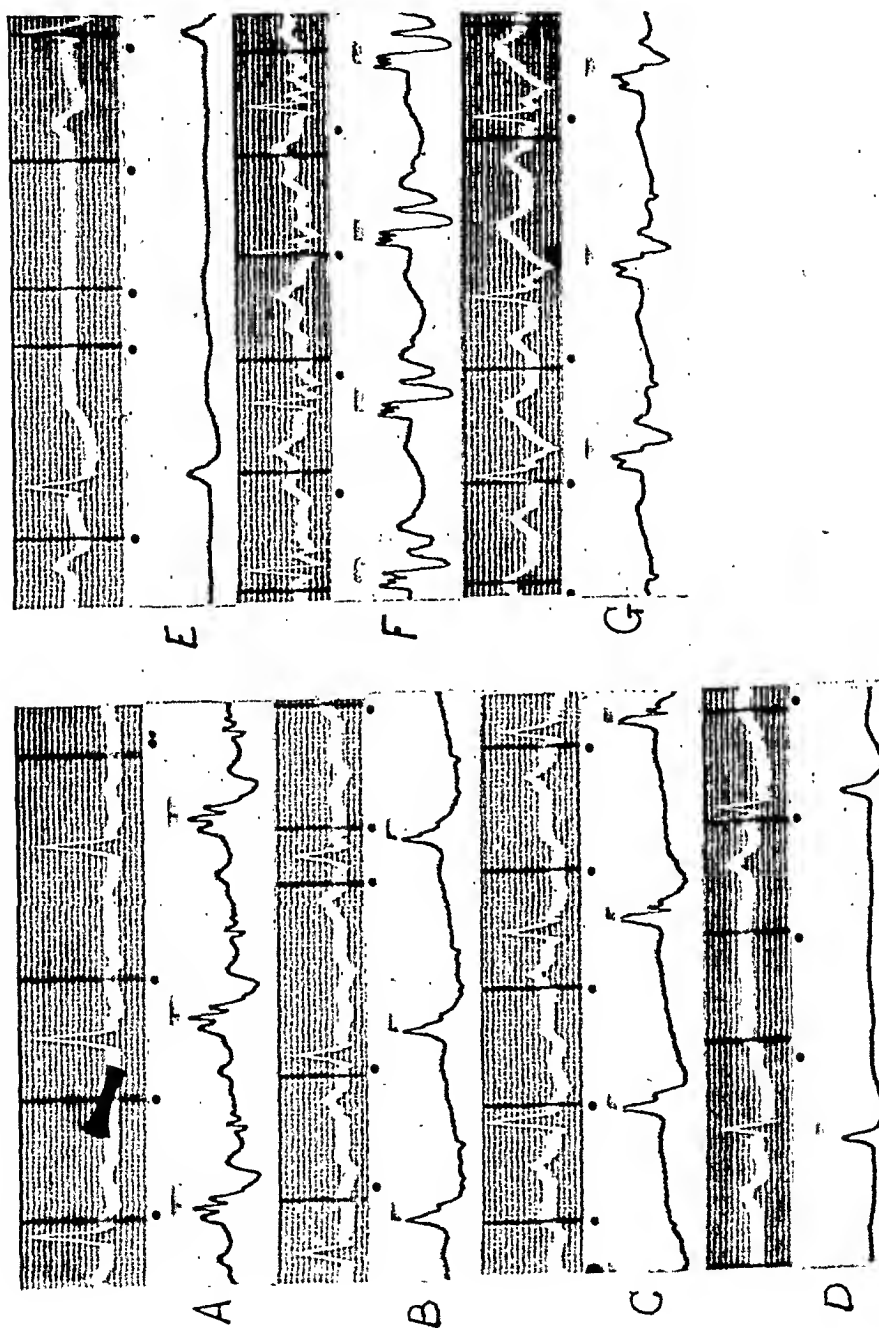


Fig. 2.—Curves obtained before, during, and after clamping of the superior and inferior venae cavae (see text).

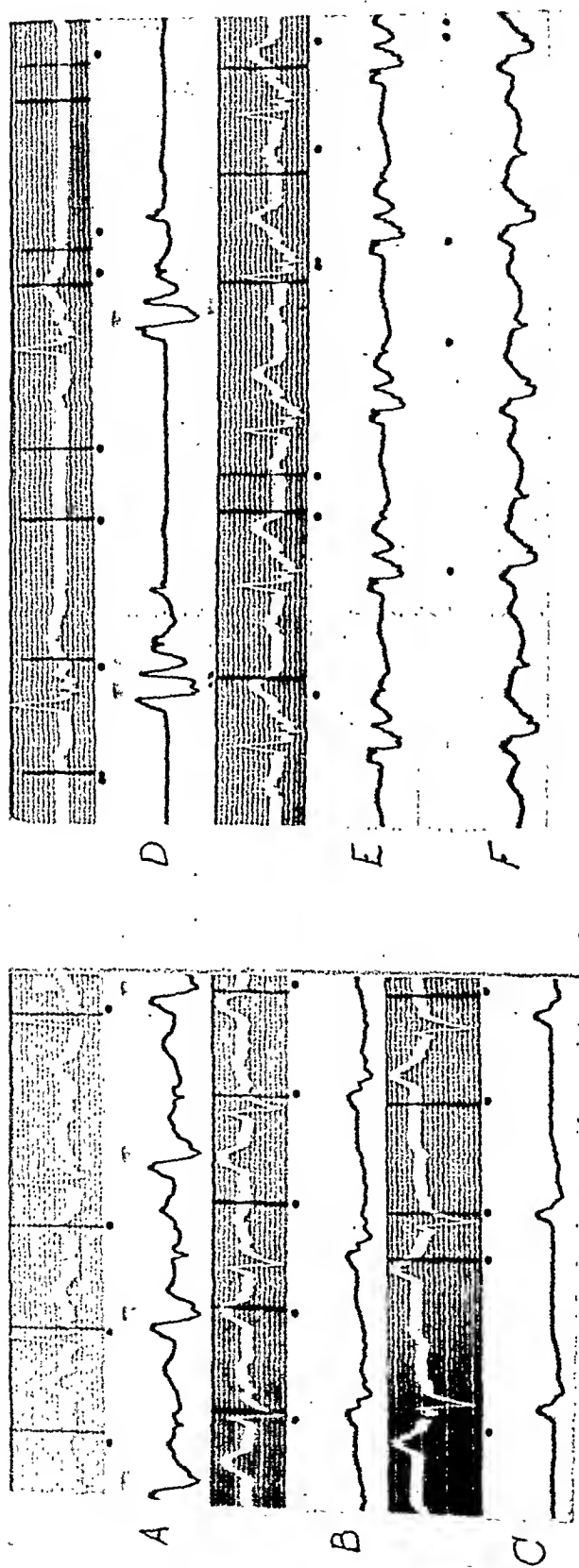


Fig. 3.—Electrocardiographic and vibrocardiographic curves obtained from the "isometrically" beating heart (see text).

and the balloons inflated. Fig. 1*B* is the tracing obtained immediately following inflation of the ventricular balloons. The second heart sound has disappeared, and the first vibration complex has become markedly altered. On auscultation, the first sound was dull and snapping in character. Figs. 1*C* and 1*D*, recorded two and four minutes, respectively, after inflating the balloons, show a persistence of vibrations synchronous with systole. Auscultation at these times revealed that the first sound became fainter as myocardial failure advanced, but it was snapping and dull in character. Almost immediately thereafter, ventricular fibrillation occurred.

Clamping of the superior and inferior venae cavae (Fig. 2) produced curves and auscultatory changes similar to those which resulted from inflation of the ventricular balloons. Fig. 2*A* was obtained from the normally beating heart before the experiment was begun. Curves *B*, *C*, and *D* were obtained immediately, one minute, and one and one-half minutes, respectively, after clamping the great veins; *E* was taken a few seconds following release of the vessels, two minutes after they had been unclamped, and *F* and *G* show a gradual return of the vibration complexes toward normal. Almost immediately after cutting off the venous flow the second heart sound disappeared. Auscultation during the period of clamping showed that the first sound was of a dull character; it became progressively more faint as the heart failed. It was seldom possible to occlude the venae cavae for more than two minutes at a time without precipitating ventricular fibrillation; however, until complete failure supervened, each systolic effort was accompanied by a sound of the character noted before.

The curves obtained after ligation of the auriculoventricular ostium, producing an "isometrically" contracting heart, are shown in Fig. 3. *A* is a control record. *B* and *C* illustrate the first vibration complex immediately, and one minute, respectively, following constriction. Auscultation revealed dull, distant sounds which were synchronous with systole. *D*, *E*, and *F* show a gradual return toward normal after release of the ligature.

In these three types of experiment the character of the sounds and the shape of the recorded vibrations bore striking resemblances to one another. In each case an audible first sound persisted until complete failure or ventricular fibrillation occurred. Occasionally, the shock incident to thoracotomy or other manipulation so affected the heart that it became weak or went into a state of failure before the experiments were begun. In such instances, any of the experimental manipulations often resulted in systolic vibrational complexes of an intensity too low to be heard.

#### COMMENT

In evaluating the results of these experiments, it is necessary to re-emphasize the fact that in all of them the factor of tensing of the





well-defined muscle vibrations were recorded while the vigor of myocardial contraction was maintained, and diminished as the muscle failed.

Doek<sup>2</sup> reported that in the heart which had been deprived of blood flow by clamping the venae cavae, or in the "isometrically" beating heart, the vibrations concurrent with systole were diminished more than 90 per cent. He believed that the small vibrations which he recorded under these conditions were merely inaudible mechanical effects of muscle contraction. These observations are at variance with our own, for our records were taken at about two times the audible threshold; furthermore, after the beginning of the experimental procedure systolic sounds were still audible. Hence, there was not a 90 per cent diminution in sound intensity. Likewise, systolic sounds were easily audible by ordinary means of auscultation, as anyone may note.

#### SUMMARY

Studies were made on the muscular elements in the first heart sound, using hearts of dogs, by eliminating normal movement and tensing the auriculoventricular valves. This was accomplished by occluding the venae cavae, by tensing a ligature around the auriculoventricular sulcus to produce an "isometrically" contracting heart, or by inflating small balloons in the ventricular cavities to pressures of 50 mm. Hg or more.

It was found that muscular sounds could be recorded and heard as long as the vigor of myocardial contraction was maintained. The possible mechanism underlying the phenomenon is discussed.

The authors wish to express their gratitude to the Burdick Corporation for their assistance in this work.

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# THE EFFECT OF INTRAVENOUS INJECTION OF PAPAVERINE HYDROCHLORIDE UPON THE MORTALITY RESULTING FROM SUDDEN OCCLUSION OF CORONARY ARTERIES IN DOGS

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IN A previous paper,<sup>1</sup> the effects of sudden occlusion of coronary arteries on conscious and anesthetized dogs were described. It was shown that, in the conscious animal, ligation of the circumflex branch of the left coronary artery resulted in a mortality of 75 per cent, and that ligation of the smaller anterior descending branch resulted in a mortality of 40 per cent. In the same paper it was reported that anesthesia (ether and morphine) reduced the mortality from 75 per cent to 25 per cent in the case of the left circumflex, and from 40 per cent to less than 10 per cent in the case of the left anterior descending branch.

We have shown, also, that unilateral and bilateral sympathetic denervation of the heart reduces the mortality.<sup>2</sup> After unilateral denervation, the mortality caused by ligation of the left circumflex branch was reduced to 33 per cent. Bilateral denervation further decreased the mortality to 10 per cent.

When ligation of either the left circumflex branch or anterior descending branch of the left coronary artery proves fatal, characteristic sequences of electrocardiographic events are always observed. Ligation of the left circumflex branch is followed by a progressive rise of the R-T segment from the isoelectric level in Lead II (Fig. 1). Extrasystoles soon appear, and are followed, after varying periods of time, by ventricular tachycardia and fatal ventricular fibrillation. When the anterior descending branch is ligated, the S-T segment becomes progressively depressed in Lead II. This is followed by extrasystoles, ventricular tachycardia, and ventricular fibrillation, in that order (Fig. 2).

From our earlier experiments we had tentatively assumed that when occlusion of a large coronary branch occurred there was also a widespread reflex spasm of the rest of the coronary arterial system, particularly of the smaller arterioles which are innervated by the vagus. It was believed that this reflex mechanism was activated by metabolites produced in the ischemic area, which, by initiating afferent impulses, gave rise to reflex efferent vagal impulses, and thus caused vasoconstriction of the medium- and smaller-sized coronary arteries. On the other hand, it is possible that certain areas of the

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myocardium are more sensitive to ischemia than others, and that ectopic beats, ventricular tachycardia, and ventricular fibrillation are more readily initiated when the blood supply to these areas is reduced.

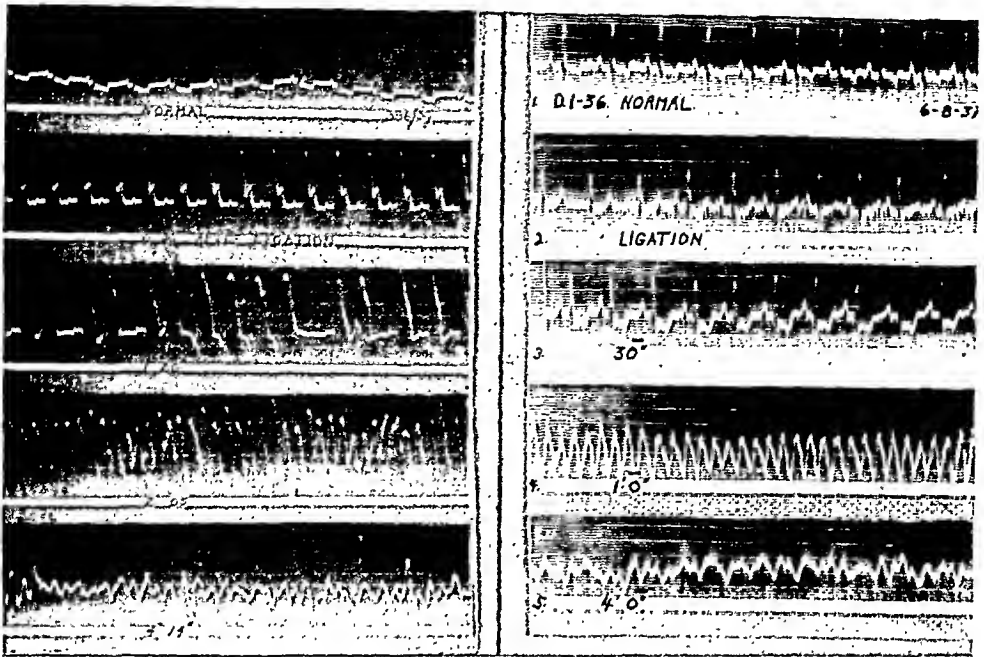


Fig. 1.

Fig. 2.

Fig. 1.—Lead II, showing changes following ligation of the circumflex branch of the left coronary artery of the conscious dog. Note the early elevation of the R-T segment. Fatal ventricular fibrillation.

Fig. 2.—Lead II, showing changes following ligation of the anterior descending branch of the left coronary artery of the conscious dog. Note the early depression of R-T segment. Fatal ventricular fibrillation.

The marked reduction in mortality achieved by anesthesia (ether and morphine), as well as by sympathetic denervation of the heart, apparently resulted from interference with the sequence of events which terminate in ventricular fibrillation. We therefore feel that the immediate treatment of angina pectoris and coronary occlusion should be directed toward (1) release of any possible spasm of coronary arteries, (2) subsequent dilatation of these vessels, and (3) depression of the fibrillation mechanisms.

In view of the fact that papaverine hydrochloride is reputed to relieve spasm in smooth muscle and also has a sedative effect, it would appear that it might help to prevent death following sudden occlusion of coronary arteries. Pal,<sup>3</sup> in his experimental investigation of papaverine, concluded that the drug relaxed smooth muscle by a direct action on the muscle fibers. He found that in arteries under normal tone the relaxing effect was negligible, but that if vasoconstriction were present this relaxing effect was quite marked. Adler<sup>4</sup> and Macht<sup>5</sup> have confirmed these observations. Macht<sup>5</sup> investigated the action of papaverine and found that it caused a marked dilatation of

the coronary, splanchnic, and peripheral vessels. He also found that it relaxed smooth muscle without producing paralysis. As an analgesic, papaverine is more effective than codeine but less effective than morphine.

In recent years there have been many reports that papaverine releases the vascular spasm which is believed to accompany arterial embolism or thrombosis. Denk<sup>6</sup> treated several patients with arterial embolism of the extremities with eupaverine (closely related to papaverine), with excellent results. Allen and MacLean<sup>7</sup> also used it successfully in one case. De Takats<sup>8</sup> has reported similar successes. More recently, De Takats, Beek, and Fenn<sup>9</sup> have advocated the use of papaverine to relieve the vascular spasm which they believe accompanies pulmonary embolism.

Because of the pharmacologic actions of papaverine, and the fact that, clinically, it is said to relieve vascular spasm, we wondered whether it might not decrease the mortality caused by occlusion of coronary arteries in conscious animals. Experiments to decide this question were undertaken. Since the mortality which resulted from ligation of the left circumflex branch was higher than that caused by ligation of the anterior descending branch, only the left circumflex was ligated in the experiments reported in this paper.

#### EXPERIMENTAL PROCEDURE

Normal, healthy dogs were used. Under intratracheal anesthesia, the thorax was opened through the fourth intercostal space and the heart exposed. A loose ligature was placed around the circumflex branch of the left coronary artery, and the ends allowed to protrude through the skin at each end of the incision in the thorax. The animals were then allowed to recover. The following day papaverine hydrochloride (11 mg./kg. body weight) was injected intravenously, and the ligation carried out on the conscious animal by traction on the ends of the loose ligature. Electrocardiograms were taken prior to operation, before and after administration of the drug, before ligation, and intermittently for some time afterward.

Twenty dogs were used in these experiments. Nine died within seventeen minutes of the ligation, and eleven survived. This gave a probable mortality of 45 per cent. One of the dogs which survived the initial ligation died about eight hours later. The remaining ten dogs survived indefinitely, so that the twenty-four-hour mortality was probably 50 per cent.

Frequently, after the intravenous injection of papaverine, the animal struggled violently for a few moments. This struggling was associated with respiratory distress, and transitory cyanosis was often observed. Following this reaction the animals lay quietly. Subsequent ligation produced evidence of cardiac pain. This pain, however, was less severe than that experienced by animals which had received no papaverine prior to ligation.

#### ELECTROCARDIOGRAPHIC CHANGES

Other than a slight bradycardia, no characteristic changes were observed in the electrocardiograms as a result of the intravenous injection of papaverine.

The electrocardiograms of the animals which died (Fig. 3) showed changes similar to those that were observed when no papaverine was administered prior to the ligation of the circumflex branch of the left coronary artery of the conscious animal (Fig. 1). In Lead II, the R-T segment showed, with varying rapidity, a progressive elevation above the isoelectric level. Extrasystoles, chiefly of right ventricular origin, appeared, and were followed by ventricular tachycardia and fatal ventricular fibrillation.

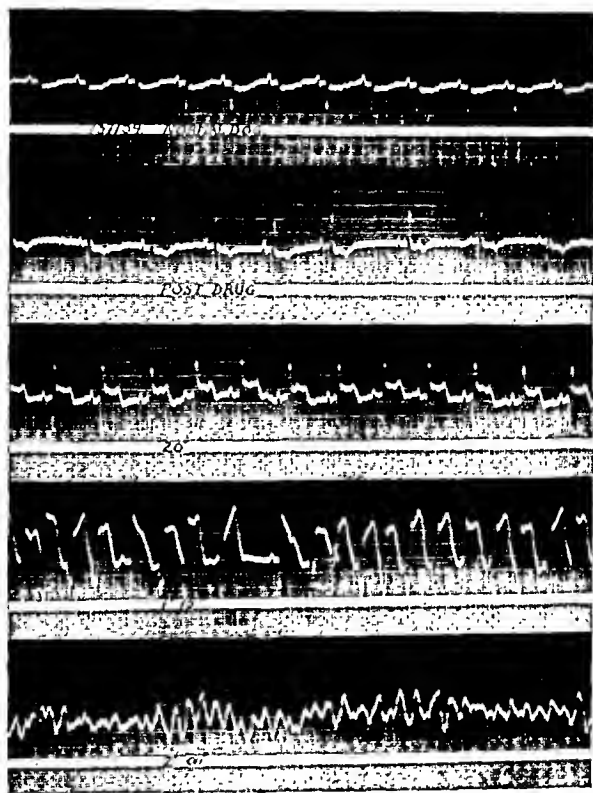


Fig. 3.—Lead II, showing changes following ligation of the circumflex branch of the left coronary artery of a dog previously injected with papaverine. Fatal ventricular fibrillation.

The electrocardiograms of the surviving animals showed, in several instances, many gross irregularities (Fig. 4). The R-T segment rose typically, and extrasystoles of both right and left ventricular origin were seen. Runs of ventricular tachycardia were observed frequently, and in four of the animals the ventricular tachycardia was fairly persistent.

#### COMMENTS

In these experiments papaverine hydrochloride was given in larger doses than have been advised for clinical use in cases of arterial embolism. However, this dose (11 mg./kg. body weight) was used so that a maximal effect could be observed.

It would appear that papaverine in the dose used reduced the twenty-four-hour mortality from 75 per cent to 50 per cent. This reduction in

mortality may have been effected by the sedative action, by the coronary dilator action, by the vascular antispasmodic action, or by any combination of these actions of papaverine.

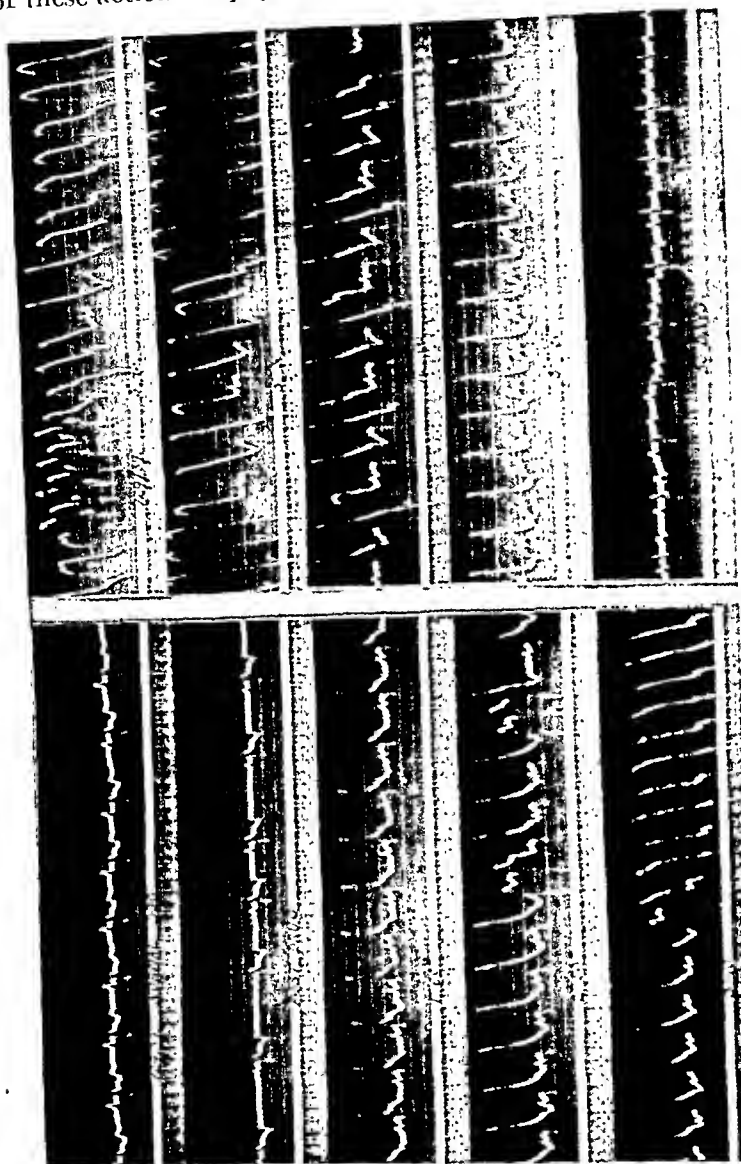


Fig. 4.—Lead II, showing changes following ligation of the circumflex branch of the left coronary artery of a dog previously injected with papaverine. Note the marked irregularities. Survived type of record.

Although the injection of papaverine does not produce any characteristic change (other than slowing) in the electrocardiogram, there were certain significant differences between the electrocardiograms of these animals after ligation of the circumflex branch of the left coronary artery and those of untreated animals which had been subjected to similar coronary artery ligation.

In the records of the latter group, the characteristic sequence of events, over a varying length of time, is progressive elevation of the R-T segment, extrasystoles, ventricular tachycardia, and ventricular fibrillation. However, when extrasystoles become numerous ventricular tachy-

cardia practically always follows, and this is usually succeeded by ventricular fibrillation. In these untreated animals, recovery after a run of ventricular tachycardia is, in our experience, rare. However, of the animals which had received papaverine, four recovered after persistent ventricular tachycardia. Although all of the animals which survived showed marked cardiac irregularities, it was apparent that the stage of ventricular tachycardia was not reached in all cases, and that, in some of those in which it was, the animal was able to recover before ventricular fibrillation ensued.

It is recognized that papaverine has a sedative action, but, in these experiments, its effectiveness as an analgesic in reducing cardiac pain, although definite, was not great.

#### SUMMARY

1. Papaverine hydrochloride, as used in these animal experiments, reduced the twenty-four-hour mortality caused by coronary artery ligation from 75 per cent to 50 per cent.

2. Papaverine hydrochloride interrupts, to some extent, the sequence of electrocardiographic events which occur after ligation of the circumflex branch of the left coronary artery.

3. Papaverine hydrochloride, even in large doses, does not completely abolish cardiac pain.

4. Papaverine hydrochloride, when injected intravenously in large doses, frequently causes respiratory distress, with cyanosis, which is not fatal.

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## THE TETRALOGY OF EISENMENGER\*

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THE number of congenital cardiac anomalies which permit survival until adulthood is relatively limited (Abbott<sup>1</sup>). Among these may be mentioned cor biatriatum triloculare, with or without transposition, and with or without tricuspid atresia; bicuspid aortic valve; coarctation of the aorta; right or double aortic arch; patent ductus arteriosus; defects of the auricular and ventricular septa, with or without congenital mitral stenosis (Lutembacher's disease); pulmonary stenosis without transposition; the tetralogy of Fallot; and the tetralogy of Eisenmenger. As has been pointed out by Abbott, many of these conditions are at the present time diagnosable by means of clinical and roentgenologic signs, and by exclusion.

We recently had the opportunity to perform a post-mortem examination on a young adult with an Eisenmenger complex. In view of the relative rarity of this condition, and because of the possibility of recognizing this type of congenital heart disease clinically, we thought that it might be of interest to report this case. Besides, this anomaly has certain aspects which may help to clarify our understanding of transposition in general. Primarily for this reason, the anatomic features of the heart are stressed, and a detailed embryologic explanation is presented.

The tetralogy of Eisenmenger, or the Eisenmeyer complex, or the tetralogy of Fallot (Eisenmenger variety) consists of (1) dextraposition of the aorta, (2) defect of the interventricular septum, (3) right ventricular hypertrophy, and (4) dilatation of the pulmonary artery. It thus differs from the tetralogy of Fallot in that there is dilatation of the pulmonary artery instead of stenosis of the pulmonary orifice.

Although the tetralogy of Fallot is not infrequently seen in hearts of adults, the tetralogy of Eisenmenger is relatively rare. Cases have been reported by Eisenmenger<sup>2</sup> (1897), Abbott<sup>3</sup> (1925), Abbott<sup>4</sup> (1927), Baumgartner and Abbott<sup>5</sup> (1929), Stewart and Crawford<sup>6</sup> (1933), Rosedale<sup>7</sup> (1935), Talley and Fowler<sup>8</sup> (1936), and Millman and Kornblum<sup>9</sup> (1936). The pertinent details of these reports are presented in Table I.

### REPORT OF CASE

A 21-year-old white man was admitted to Michael Reese Hospital Nov. 3, 1939, and died the same day. He was born a blue baby, and had been an invalid all of his life because of dyspnea on moderate exertion. His early development was retarded; at the age of 2 he was unable to walk or talk. He managed to reach the eighth grade of grammar school. He was subject to frequent sore throats, and, at the age

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TABLE I  
CASES OF EISENMENGER COMPLEX PREVIOUSLY REPORTED

AUTHOR	DATE	AGE	SEX	PERTINENT CLINICAL DATA	POSITION OF AORTA	OTHER IMPORTANT PATHOLOGIC CHANGES	CAUSE OF DEATH
Eisenmenger	1897	32	M	Cyanosis during youth, with some dyspnea on exertion. Slight clubbing of fingers. Systolic murmur over middle of heart, not heard above its base nor along the course of the aorta, but transmitted to the right and inferiorly and to the apex. Diastolic murmur at lower end of sternum in terminal stage.	Riding aorta	Ductus arteriosus closed. No coarctation. Foramen ovale closed.	Heart failure
Abbott (Libman)	1925	33	M	Heart trouble at age of 5. Dyspnea and pain in chest on admission to hospital. Loud, rough, systolic murmur heard over entire precordium, with maximum intensity within left nipple line. P <sub>2</sub> not accentuated. Systolic thrill at apex. Some clubbing of fingers.	Riding aorta	Slight coarctation of the aorta. Possibly congenital aneurysm of the membranous septum. Old endocarditis of the aortic valve, with insufficiency. Old endocarditis of the mitral valve. Subacute bacterial endocarditis involving aortic and mitral valves and defect of interventricular septum present in the aneurysm. Foramen ovale closed.	Subacute bacterial endocarditis
Abbott	1927	Eight cases of dextroposition of the aorta without stenosis of the pulmonary artery and two showed hypoplasia of the aorta. Mention is made of an infant, aged 15 months, with the typical Eisenmenger complex.					
Baumgartner and Abbott	1929	20	M	Lack of endurance, dyspnea on exertion, cyanosis for some time. Hoarseness and aphonia. For 7 years, loud, harsh, systolic murmur over pulmonic area. Diastolic murmur to left of sternum.	Riding aorta	Pulmonary cusps of unequal size, with fenestration. Small accessory coronary artery, arising from pulmonary artery. Slight conus stenosis. Thick muscle bundles of conus. Paradoxical embolus, with brain abscess.	Paradoxical embolus

Stewart and Crawford	1933	60	M	No dyspnea or cyanosis during life. No clubbing of fingers. Marked terminal cyanosis, with dyspnea. Soft, blowing, systolic murmur at apex. Hypertension. Marked right and left ventricular failure.	Riding aorta	Healed pulmonary valvulitis and arteritis.	Heart failure
Rosedale	1935	10	M	Transient cyanosis at birth. Cyanosis and dyspnea on exercise thereafter. Moderate clubbing of fingers. Systolic murmur at apex.	Riding aorta	Patent foramen ovale. Ductus arteriosus closed. Hypoplasia of the aorta.	Heart failure
Talley and Fowler	1936	31	F	Blue baby. Dyspnea on exertion throughout life. Cyanosis became worse after two pregnancies. Marked clubbing of fingers. Hoarseness for many years. Systolic, and, at times, diastolic thrill at midsternum. Diastolic thrill sometimes at third left intercostal space. Low-pitched diastolic murmur constantly heard at pulmonary region, which could be traced down to apex. Systolic murmur also heard at apex and midsternum, but not transmitted to base.	Riding aorta	Hypoplasia of the aorta. Hypertrophy of crista. Pulmonary cusps thickened and rounded.	Heart failure
Millman and Kornblum	1936	32	F	Slight cyanosis, slight clubbing of fingers. Double thrill—systolic and diastolic—at pulmonic area. Loud, rough, systolic murmur, with slight diastolic phase, at pulmonic, transmitted slightly to clavicle. P <sub>2</sub> not heard.	Riding aorta	Subacute bacterial endocarditis of the pulmonic valve. Foramen ovale closed.	Subacute bacterial endocarditis

of 10, had joint pains with no accompanying fever. He had never received medical care until two weeks before admission, when his dyspnea became more marked. A physician prescribed digitalis, but the patient became worse and was sent to the hospital. On admission his pulse was imperceptible; the temperature was 101°, and the respiratory rate was 40 per minute. His blood pressure could not be measured. He was poorly developed and undernourished, orthopneic, dyspneic, cyanotic, restless, perspiring, and too weak to answer questions. There was marked clubbing of the fingers and toes. The throat was injected, with prominent vessels about the large, cryptic tonsils. Three petechiae were seen on the soft palate. A few râles were present at the base of the right lung. There was bulging of the lower end of the sternum. The heart was enlarged; its transverse diameter extended from the left axillary to the right midclavicular line. There was marked prominence of the pulmonary conus, in which region a diastolic thrill was felt and a loud blowing systolic murmur was heard. A blowing murmur was also heard at the apex; it was difficult to time because of the rapid rate (166). Heart tones were audible along the entire spine. The liver was enlarged, extending to the umbilical region, and was firm and very tender. The spleen was not palpable.

The patient died suddenly, five hours after admission. The clinical diagnoses were: congenital heart disease (tetralogy of Fallot); rheumatic stenosis of the mitral orifice, with insufficiency of the valve and enlargement of the left auricle; congestive heart failure, with auricular fibrillation. Subacute bacterial endocarditis was also considered.

#### POST-MORTEM EXAMINATION

*Heart* (Figs. 1, 2, and 3).—The heart was markedly enlarged to the right and left; its transverse diameter was two-thirds that of the chest cavity, and it weighed 450 Gm. The apex was formed by the right ventricle. From the base two vessels were seen to emerge, a smaller to the right and slightly anterior, and a larger to the left and somewhat posterior. Many single and confluent, opaque, grayish-white patches were present on the pericardial surface of the base of these two vessels. Two auricular appendages were noted adjacent to each other on the right anterior aspect of the heart, one lying superior and to the left of the other. The mutual relationships of the various heart chambers were normal.

The right auricle was moderately dilated and its wall distinctly thickened, measuring as much as 0.3 cm. in thickness. The superior and inferior venae cavae and the coronary sinus entered this chamber normally. The eustachian and thebesian valves were normal. The limbus, instead of the usual arc, with a large horizontal diameter, presented an arc with an enlarged vertical diameter. The foramen ovale was closed, and there was no defect of the auricular septum. It was now noted that the auricular appendage which lay inferior and to the right was the right auricular appendage. The endocardium of the right auricle presented no remarkable changes.

The tricuspid orifice measured 14.5 cm. in circumference. The leaflets of the tricuspid valve, although normally formed, were somewhat thickened. The corresponding chordae tendineae were likewise somewhat thickened, but presented no further change. There was no posterior papillary muscle; the anterolateral papillary muscle was normal.

The right ventricular chamber was distinctly larger than normal. Its wall measured 1.2 cm. in thickness. From the base of the ventricle the two vessels noted externally emerged, each with its own ventricular outflow portion. The artery to the right and slightly anterior was the aorta, and the one to the left and slightly posterior was the pulmonary artery. The aortic orifice measured 8 cm. in circumference. The aortic valve consisted of three well-formed cusps, one situated to the

left, one anterior and to the right, and one posterior and to the right. The non-coronary cusp was the right anterior. The aortic cusps were markedly fenestrated throughout, and thickened at their line of closure. The aorta gave off the brachiocephalic vessels normally. In the region of the distal part of the isthmus, the lumen



Fig. 1.

Fig. 2.

Fig. 1.—Right ventricular view of the heart, exposing the mouth of the aorta. Note the aorta coming off the right ventricle, the septal defect just below the aortic valve, and the leaflets of the tricuspid valve.

Fig. 2.—Right ventricular view of the heart, exposing the infundibulum. Note the muscular arch separating the infundibulum from the outlet of the right ventricle leading into the aorta (above the glass rod).



Fig. 3.—Left ventricular view of the heart. Note the interventricular septal defect and the stenosis of the mitral orifice (not opened).

of the aorta was distinctly constricted, measuring only 5 cm. in circumference. The ductus arteriosus was widely patent. The bronchial arteries were not enlarged. The circumference of the descending aorta was distinctly diminished. The orifice of the

pulmonary artery measured 9.6 cm. in circumference. It was thus distinctly larger than the aorta. Its valve consisted of three cusps—one right, one anterior and to the left, and one posterior and to the left. The cusps showed no remarkable changes. The lumen of the pulmonary artery was larger than that of the aorta. The two pulmonary arteries arose normally.

The topography of the muscle bundles of the right ventricle was distinctly abnormal. The *moderator band* was thick, and merged with the septal muscle bundle, which was likewise markedly thickened. This bundle ascended obliquely upon the septum toward the base of the ventricle, where it formed an arch of muscle over the roof of the ventricle; this arch then descended obliquely and laterally over the anterior wall of the right ventricle. Thus the septal muscle bundle formed a complete arch which separated the two outflow portions of the right ventricle. The parietal muscle bundle, however, was not present. The *pars membranacea septi ventriculorum* was absent. The adjacent musculature of this septum was likewise defective, producing an opening in the interventricular septum which measured 2 cm. in its greatest diameter. The defect faced the aorta, and was separated from the outflow portion of the pulmonary artery by the arched musculature of the septal muscle bundle.

The left auricular chamber was not as large as the right; its wall measured 2 mm. in thickness. It received the four pulmonary veins normally. The left auricular appendage was not present in its normal position to the left of the normally placed aorta, but emerged from a more posterior position to the right of the dextraposed aorta. This was the abnormal appendage which was seen superiorly and to the left of the right auricular appendage on the anterior wall of the right auricle.

The mitral valve leaflets and their corresponding chordae tendineae and papillary muscles were normally formed. However, the leaflets were markedly thickened at their line of closure, and were mutually adherent, as were their chordae, thus producing a funnel-shaped opening of the mitral orifice which measured only 4.5 cm. in circumference.

The left ventricular chamber was about normal in size. Its wall measured 1.1 cm. in thickness. Numerous, atypical chordae bridged the cavity of this chamber; they originated from the papillary muscles and were inserted on the septum. The only outlet from this chamber was the defect in the interventricular septum. The rim of this defect presented a thickened endocardium on its left ventricular aspect which formed a ledge, especially in its inferior portion.

The left coronary artery arose from the right posterior sinus of Valsalva. The right coronary artery was represented by two separate vessels, each with a separate ostium; both ostia arose from the left sinus of Valsalva. The left coronary artery gave rise to a branch which passed obliquely downward over the right ventricle toward the apex, and terminated some distance above the apex. The remainder of the left coronary artery formed a small branch which ran in an oblique direction to the superior wall of the right ventricle. The larger, right coronary artery curved around the posterior wall of the pulmonary artery, gave off branches to the septum, and then divided into an anterior descending branch and a large *ramus marginis obtusi*. The smaller, right coronary artery ran in the anterior atrioventricular sulcus to the acute margin of the heart; it gave off the *ramus anterior ventriculi dextri*, and terminated as the *ramus acutus*. There was no posterior descending branch.

The diagnoses, as far as the heart was concerned, were: (1) partial transposition of the great arterial trunks (Rokitansky), transposition type II (Spitzer), tetralogy of Eisenmenger; (a) origin of the aorta and pulmonary artery from the right ventricle; (b) defect of the interventricular septum; (c) dilatation of the pulmonary artery; (d) coarctation of the aorta; (e) patency of the ductus arteriosus; (f) abnormally formed left auricular appendage; (g) atypical coronary artery distribution; (h) abnormal topography of the musculature of the right ventricle;

(2) old endocarditis of the mitral valve, with insufficiency of the valve and stenosis of its orifice; and (3) hypertrophy of the heart—right auricle and ventricle, marked, and left auricle, moderate.

In addition, there were (1) moderate kyphoscoliosis, (2) moderate emphysema, (3) chronic passive hyperemia of the lungs, liver, spleen, kidneys, and gastrointestinal tract, and (4) clubbing of the fingers and toes.

## COMMENTS

The knowledge that certain anomalies occur together leads us to attempt to discover symptoms, physical signs, and other data which may enable us to make a correct clinical diagnosis and an accurate prognosis, and to institute intelligent treatment. Pathologically, the knowledge that a complex exists is the starting point for an investigation of the embryologic variant in the development of the heart which was responsible for the anomaly.

Thus, the realization by Farre,<sup>10</sup> Peacock,<sup>11</sup> and Fallot<sup>12</sup> that dextro-position of the aorta, a defect of the ventricular septum, pulmonary stenosis, and right ventricular hypertrophy represent a pathologic complex, and constitute the most frequent anomaly found in adults, eventually made the clinical diagnosis possible. Likewise, the realization that there may be dilatation of the pulmonary artery instead of the more usual stenosis has led to the possibility of differentiating clinically between the tetralogy of Eisenmenger and that of Fallot. Clinically, the most important differences between the two conditions are as follows: (1) there are relatively less cyanosis and clubbing of the fingers in cases of the Eisenmenger complex; (2) hoarseness may occur in cases of the Eisenmenger complex, but not with the tetralogy of Fallot (Baumgartner and Abbott,<sup>5</sup> Talley and Fowler<sup>8</sup>); (3) pulmonic insufficiency, with a diastolic murmur, occurs in some cases of the Eisenmenger complex, but not with Fallot's tetralogy (Baumgartner and Abbott,<sup>5</sup> Talley and Fowler,<sup>8</sup> Millman and Kornblum<sup>9</sup>); (4) accentuation of the pulmonary conus, as shown roentgenologically and by percussion, is much more marked with the Eisenmenger complex than with the tetralogy of Fallot, and the silhouette resembles that caused by uncomplicated auricular and large ventricular septal defects, and, to a lesser extent, by an auricular septal defect with mitral stenosis (Lutembaecker's disease); (5) there is possibly a difference in the transmission of the systolic murmur in the two conditions. In the case reported by Eisenmenger, the murmur was heard over the middle of the sternum, and was transmitted to the right, inferiorly, and to the apex, but not to the neck. The transmission was similar in the case of Talley and Fowler. In the cases of Millman and Kornblum, and Baumgartner and Abbott, the systolic murmur was heard at the pulmonic area, and, in the former, was transmitted slightly to the clavicle (left?). In the case reported by Abbott, the systolic murmur was heard over the entire precordium, and was of maximum intensity over the left nipple. In the cases of Stewart and Crawford, and Rosedale, a systolic murmur was heard over the apex. No mention is

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made of lack of transmission of the murmur to the neck in any of the cases except that of Eisenmenger. V. Schroetter<sup>13</sup> (who detected the absence of pulmonary stenosis in the case of Eisenmenger) considered that, when there is a ventricular septal defect with stenosis, the murmur may be transmitted to the neck because of flow of blood from the right to the left ventricle, whereas, if the defect were unaccompanied by stenosis, the flow of blood would be from left to right (except in the terminal phase), and therefore the murmur would not be transmitted to the neck. It is possible that this may be a differentiating point between the tetralogies of Fallot and Eisenmenger. There are, however, at the present time insufficient data to draw definite conclusions on this point.

There are relatively less dyspnea and cyanosis with the Eisenmenger complex because, as Baumgartner and Abbott stated, the anatomic conditions are more favorable for oxygenation than is the case with the Fallot anomaly. In Eisenmenger's anomaly the aerated blood is carried from the left ventricle into the aorta directly (in riding aorta), or through the defect in the ventricular septum (as in our case). Because the arch of musculature at the base of the right ventricle demarcates the outflow tracts of the aorta and pulmonary artery, relatively little of this aerated blood gets into the pulmonary artery. The amount of unaerated blood which reaches the aorta varies with the position of the aorta. The unrestricted flow of blood through the pulmonary artery presents a marked contrast to Fallot's tetralogy, in which oxygenation in the lungs is insufficient because of the stenosis of the pulmonary orifice.

The hoarseness which occurs in some cases is caused by encroachment of the markedly dilated pulmonary artery on the recurrent laryngeal nerve, as pointed out by Talley and Fowler.<sup>8</sup>

It must be remembered that Eisenmenger regarded his case as one of uncomplicated patency of the interventricular septum. From his description of the relation of the pulmonary artery and aorta to the patency of the ventricular septum, it is quite clear that he was dealing with a riding aorta (Rokitansky), or type I transposition (Spitzer). Eisenmenger, however, overlooked this fact, which was later brought out by Abbott. Thus it is to Abbott that we owe the conception of what we now call the tetralogy of Eisenmenger, and not to Eisenmenger himself.

#### PATHOGENESIS OF THE EISENMENGER COMPLEX

From the pathologic standpoint, our understanding of this combination of anomalies has gone hand in hand with our conception of transposition. Since the time of Rokitansky<sup>14</sup> it has been generally agreed that in transposition complexes the primary anomaly is the transposition of the arteries, and, therefore, in the Eisenmenger complex the defect

in the ventricular septum and the dilatation of the pulmonary artery should be considered secondary. According to the theory of Rokitsansky, the underlying embryologic variant in this complex is an abnormality in the rotation of the septum bulbi.

According to the theory of Spitzer,<sup>15</sup> this complex represents a sub-type of transposition type I or type II. Because of lack of sufficient torsion of the bulboventricular loop, migration and fusion of both primary bulbar septa are incomplete, with the result that the right ventricular aorta reopens. This, in turn, works to the disadvantage of the left aorta, which becomes obliterated. Thus, in the Eisenmenger complex, according to Spitzer, the aorta would have to be either a reopened right ventricular aorta, or an as yet incompletely obliterated left aorta; if it were the latter, it would mean that the right aorta had not yet reopened.

In 1937, we reported six cases of transposition of the large arteries, with a complete summary of old and recent theories of transposition.<sup>16</sup> We pointed out our objections to the theories of Rokitsansky,<sup>14</sup> Spitzer,<sup>15</sup> Keith,<sup>17</sup> and Pernkopf and Wirtinger.<sup>18</sup> We agreed, however, with the underlying hypothesis of Keith, namely, that transposition of the large arteries is caused by an abnormality in the absorption of the bulbus. Using the studies of Pernkopf and Wirtinger<sup>18</sup> on the movement of the heart during development as a basis, we formulated our own theory of transposition.

Pernkopf and Wirtinger<sup>18</sup> showed that the movements of the heart during development normally may be divided into two phases. The first phase is concerned with the formation of the auriculoventriculobulbar loop and the bulbar bayonet. At the end of this phase the bulbar ridges assume a spiral course of  $270^\circ$ . The large arteries, however, are not as yet twisted about each other. The second phase is concerned with the absorption of the bulbus. This is brought about by two processes. Torsion of  $150^\circ$  (counterclockwise, looking truneward from the bulbus) occurs at the distal bulbar ostium, which is accompanied by back torsion of  $45^\circ$  (clockwise, looking bulbward from the ventricle) at the proximal bulbar ostium. The twist of the bulbar ridges is thus reduced, and given to the truncus septum. The bulbus is shortened and absorbed into the ventricle, and the arterial trunks now take on their definitive twist of  $150^\circ$  about each other.

We postulated that transposition is produced by an abnormality in the execution of the second phase, which, in turn, is caused by an abnormality in the bulboauricular spur area. This permits an increased back torsion at the proximal ostium, which thus diminishes the necessity for torsion at the distal ostium. This results, grossly, in transposition.

Recently, after a study of truncus arteriosus communis persistens,<sup>19</sup> we re-evaluated our theory of transposition. We concluded that our fundamental hypothesis that we were dealing with an abnormality in the absorption of the bulbus was correct. However, we felt we had erred



as to the primary cause for this abnormal absorption. This is, most likely, not an abnormality in the bulboauricular spur, which we now regard as secondary, but an abnormality in the formation of ridge 3B.

Ridge 3B is phylogenetically the most recent formation in the bulbus, and is present only in birds and mammals. In the bulbus of the reptile, in addition to ridge 1A (which is present from the lungfish up), two opposite ridges are formed, namely, ridges 4B and 3C. In the transition from the reptile to the mammal, ridge 3B was apparently formed by the fusion of ridges 4B and 3C. Thus, whereas in the reptile the bulbus is divided into three parts, in the mammal it is divided into only two parts. The same is true of the truncus. Whereas in the reptile a septum aorticum and septum aorticopulmonale are formed, in the mammal only a single septum aorticopulmonale develops.

### Normal and Abnormal Absorption of the Bulbus

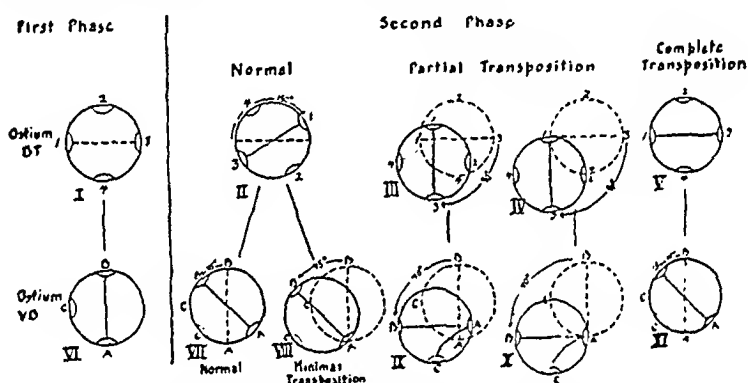


Fig. 4.—Absorption of the bulbus in transposition. There is an abnormality in the formation of ridge 3B, whereby it is poorly formed or replaced by ridge 4B or 3C. This results in decreased torsion at the distal ostium. In addition, this torsion occurs either around cushion 1, or close to cushion 1. At the proximal ostium, back torsion occurs around cushion A or close to cushion A. This back torsion may be 45°, or may reach 90°; the latter is normal in an earlier stage.

I, 2, 3, 4, Distal bulbar cushions; A, B, C, proximal bulbar cushions; BT, bulbo-truncare (ostium); VB, ventriculobulbare (ostium); I, VI, distal and proximal bulbar ostia, respectively, at the end of the first phase (normal, and in transposition); II, VII, distal and proximal bulbar ostia during the second phase of normal absorption of the bulbus; II, VIII, bulbar ostia in transposition, with congenital aneurysm of the membranous septum during the absorption of the bulbus; III, IX, bulbar ostia in partial transposition during the absorption of the bulbus, when torsions center close to cushions 1 and A; IV, X, bulbar ostia in partial transposition during the absorption of the bulbus, when torsions center about cushions 1 and A; V, XI, bulbar ostia in complete transposition when no torsion occurs at the distal ostium, while mild back torsion occurs at the proximal ostium.

These differences within the embryonic truncus and bulbus result in gross differences in the definitive forms. Thus, in the reptile, the bulbus is absorbed almost completely, producing right and left ventricular aortae and a pulmonary artery with a defect of the ventricular septum; only a rim of bulbus musculature persists (Greil<sup>20</sup>). In the mammal, however, it is completely absorbed, which joins the pulmonary artery to the right ventricle and the aorta to the left ventricle, and closes the interventricular septum.

Transposition of the large vessels may be defined as that anomaly which occurs when the embryo of the mammal fails to carry out its most recent phylogenetic development, namely, the formation of ridge 3B

(Fig. 4). Instead, it retains either ridge 4B or 3C, forms an incomplete ridge 3B, or possesses only a solitary ridge 1A. The absorption of such a bulbus then proceeds abnormally. Because of either the absence of an opposite ridge, or lessened twist of the opposite ridge (either 4B or 3C), less torsion occurs at the distal ostium, and the torsion is excentric; the center of torsion is at a point between the center and cushion 1, or at cushion 1. The back torsion at the proximal ostium also occurs excentrically about a point between the center of the bulbus and cushion A, or about cushion A. This throws the aorta to the right, producing a riding aorta, or both the aorta and pulmonary artery emerge from the right ventricle, which constitutes partial transposition. In complete transposition, we postulate that, in addition to the absence of ridge 3B, ridge 1A either primarily fails to form, or secondarily becomes obliterated by the blood current. The absorption of such a bulbus, without ridges except at the proximal and distal bulbar ostia, consists purely of a process of telescoping and shrinkage, without torsions. This joins the aorta and pulmonary artery to the wrong ventricles.

#### ANALYSIS OF OUR CASE

The anatomic characteristics of our case were as follows: (1) both the aorta and pulmonary artery emerged from the right ventricle; (2) the diameter of the aorta was less than that of the pulmonary artery; (3) no artery emerged from the left ventricle, and, therefore, its only outlet was a defect in the interventricular septum; (4) coarctation of the aorta was present; (5) the ductus arteriosus was widely patent; (6) the left auricular appendage was abnormally formed and situated; (7) the coronary arterial ostia were displaced about  $105^\circ$  counterclockwise; (8) the coronary arterial distribution was abnormal; and (9) the muscle bundles of the right ventricle showed an abnormal configuration.

The fact that both the aorta and pulmonary artery arose from the right ventricle signified that we were dealing with a partial transposition (transposition type II, of Spitzer, or our Type C). The position of the coronary ostia showed that, during the second phase of the development of this heart (i.e., during the absorption of the bulbus), only  $45^\circ$  of torsion had occurred at the distal ostium, instead of the normal  $150^\circ$ . Also, according to our interpretation, this incomplete torsion at the distal ostium took place excentrically around cushion 1, or close to cushion 1 (Fig. 5). At the proximal ostium, back torsion also occurred excentrically around, or close to, cushion A. This caused both the aorta and pulmonary artery to arise from the right ventricle.

The reason for this abnormal absorption of the bulbus was that the mammalian ridge 3B failed to develop. Instead, the reptilian ridge 4B was formed. This produced, on the one hand, the abnormality in the absorption of the bulbus, and, on the other hand, the inequality in the size of the two arterial vessels (small aorta and large pulmonary

artery, Fig. 5). In the tetralogy of Fallot we believe that the reptilian ridge 3C is formed, thus producing a small pulmonary artery and a large aorta.

### Absorption of the Bulbus in the Normal and in the Eisenmenger Complex

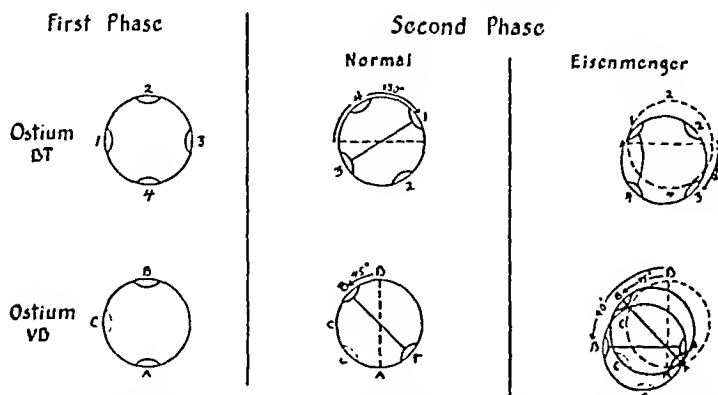


Fig. 5.—Absorption of the bulbus in the normal heart and in the Eisenmenger complex. Because of the formation of ridge 4B instead of 3B, a definitive bulbar septum, which consists of 4-1 at the distal ostium and A-B at the proximal ostium, develops. Because of the abnormal ridge 4B, the absorption of the bulbus proceeds abnormally. Normally, during this process there are a torsion of 150° (in the direction of the arrow) at the distal ostium, and a back torsion of 45° (in the direction of the arrow) at the proximal ostium. These torsions center around the bulbus. In the Eisenmenger complex, less torsion occurs at the distal ostium (BT'), and this centers around cushion 1. Back torsion of 45° to 90° centers at the proximal ostium, around cushion A.

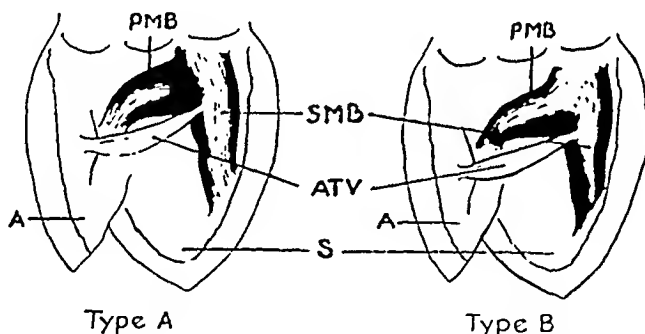


Fig. 6.—Normal topography of the muscle bundles of the right ventricle. *Type A*, Two distinct muscle bundles are noted. *Type B*, An arch of musculature is present at the base of the pulmonic valve.

SMB, Septal muscle bundle; PMB, parietal muscle bundle; ATV, anterior tricuspid leaflet; A, Anterior wall of the right ventricle; S, septal wall of the right ventricle.

A possible means of verifying this theory may be found by studying the topography of the muscle bundles. In our original work on transposition, because of confusing nomenclatures and conflicting conceptions of the muscle bundles of the right ventricle, we studied these muscle bundles in thirty-seven hearts from newborn infants. Two types of topography were noted (Fig. 6). In twenty-one cases there were two distinct muscle bundles, as pointed out by Keith.<sup>24</sup> From the septal cusp of the pulmonic valve, a muscle bundle descended obliquely over the septum toward the apex. This we called the septal muscle bundle. Near the apex it gave off the moderator band. On the anterior wall of

the right ventricle, the parietal muscle bundle ascended toward the base of the heart in close proximity to the anterior leaflet of the tricuspid valve. The superior portion of the muscle terminated at the septal cusp of the pulmonie valve. Its main intermediary portion fused with the musculature of the septum beneath the septal muscle bundle. There was a distinct raphe where the parietal muscle bundle dipped behind the septal muscle. The inferior portion terminated at the base of the anterior leaflet of the tricuspid valve. In the remaining sixteen cases there was a mass of musculature which formed an arch over the base of the ventricle at the base of the septal cusp of the pulmonie valve, with fibers radiating over the anterior wall of the right ventricle, adjacent to the



Fig. 7.—Muscle bundles of the right ventricle in the tetralogy of Fallot. The septal muscle bundle is hypertrophied. The parietal muscle bundle is minute or absent.

tricuspid, and down over the wall of the septum. In the human heart, therefore, it appears that we are dealing with two separate formations, namely, a parietal and a septal muscle bundle, and that these may become secondarily fused. Judging from the studies of Keith,<sup>24</sup> and Pernkopf and Wirtinger,<sup>18</sup> the formation of the parietal muscle bundle is related to that of the proximal bulbar septum, and is correlated with the presence and downward growth of ridge 3B. It is derived from cushion B, the bulboauricular spur, and the counter-ridge BO of the interventricular septum. The septal muscle bundle, according to Spitzer,<sup>15</sup> Fuchs,<sup>21</sup> Benninghoff,<sup>22</sup> Tandler,<sup>23</sup> and Keith<sup>24</sup> (with Pernkopf and Wirtinger<sup>18</sup> dissenting), is derived from ridge A, or C in A (see Spitzer).

The character of the muscle bundles of the right ventricle in congenitally abnormal hearts therefore affords us information concerning what took place during embryonic life. Spitzer<sup>15</sup> first pointed this out, and Humphreys<sup>25</sup> and we<sup>16</sup> have confirmed it. In the tetralogy of Fallot and trunco communis persistens, the septal muscle bundle is hypertrophied, while the parietal muscle bundle is small or almost absent (Fig. 7). In the tetralogy of Eisenmenger, however, there is often an arch of musculature over the base of the right ventricle which separates the outflow regions of the aorta and pulmonary artery (Fig. 2). In general, it has the topography of the normal, fused, septal and parietal muscle bundles, except that the parietal muscle bundle has no relationship to the anterior tricuspid leaflet, as is normally the case. This was noted by us in Case 2 of our series of transpositions, and occurred in the case reported herein; it was also present in the heart described by Talley and Fowler.<sup>8</sup> No adequate description of the muscle bundles is given by the other authors. Our previous interpretation was that this muscle bundle was purely a hypertrophied septal muscle bundle. It is now apparent to us that this arch of musculature incorporates an element of ridge 4B; therefore, it is the bulbar septum which has remained, demarcating that portion belonging to the aorta from that portion belonging to the pulmonary artery. If this is so, we are now able to locate point B, and to demonstrate that torsion at the proximal ostium occurred more or less around cushion A, which accounts for the fact that the aorta arose from the right ventricle. In the tetralogy of Fallot, however, the parietal muscle bundle is small or absent, because the opposite ridge in this case is 3C, not 4B. In transposition there may also be increased back torsion, amounting to 90°, at the proximal ostium about cushion A. Normally, such back torsion originally occurs during the second phase, but is secondarily reduced to 45°.

The defect of the interventricular septum in the Eisenmenger complex is caused by the rotation of cushion B, which makes approximation of the proximal bulbar septum with the interventricular septum and the endocardial cushions impossible. The atypical coronary distribution is characteristic of various types of transposition; this has been thoroughly discussed by Spitzer.<sup>15</sup> The coarctation of the aorta, because of the accompanying anomalies, may be called the infantile type, and may be considered as part of the general hypoplasia of the aorta. This was also true in the case of Abbott.<sup>3</sup> A discussion of this coarctation is beyond the scope of this communication. The ductus arteriosus remained patent because of a difference in pressure between the pulmonary artery and the hypoplastic aorta.

The abnormal position of the left auricular appendage was a result of the abnormality in the absorption of the bulbus. Normally, during the second phase, the mesocardial (aortic) portion of the bulbus sinks into the auricular canal region, and thus the left auricular appendage comes to lie to the left of the aorta, and behind and to the left of the

pulmonary artery. The abnormal absorption of the bulbus in this heart, the rotation of cushion B ventrally, and the large size of the pulmonary artery displaced the auricular appendage to the right of both the aorta and the pulmonary artery.

It is of interest that, in most cases of Eisenmenger's complex, the aorta is a riding aorta. Ours was an exception, in that there was a partial transposition, or transposition type II of Spitzer (our type C). In this particular respect it is also of interest that in the case of Abbott<sup>3</sup> there was an aneurysm of the membranous septum. In a previous communication we<sup>26</sup> pointed out that in some (if not in all) cases of aneurysm of the membranous septum transposition is also present. The case of Abbott<sup>3</sup> bears out our original impression. This case was very similar to that of Eakin and Abbott<sup>27</sup> (transposition, infundibulum stenosis, and aneurysm of the membranous septum) (tetralogy of Fallot), except that in the case of Libman and Abbott there was no infundibular stenosis. Thus, both the tetralogy of Eisenmenger and that of Fallot may be classified according to types A, B, and C of our classification, in which A is transposition, with aneurysm of the membranous septum; B, transposition, with a riding aorta; and C, partial transposition, with the aorta and pulmonary artery arising from the right ventricle.

Our case differs from those already reported, in that, in addition to the congenital lesions, there was an old endocarditis, with stenosis of the mitral orifice. In the case of Abbott<sup>3</sup> there was also an old endocarditis of the mitral and aortic valves, but no stenosis was present.

The cause of death in cases of the Eisenmenger complex is usually heart failure, of which our patient died. The patients of Abbott<sup>3</sup> and Millman and Kornblum<sup>9</sup> died from subacute bacterial endocarditis.

#### SUMMARY

A case of the tetralogy of Eisenmenger is presented. The literature pertaining to this complex is reviewed, and the clinical differentiation of this anomaly from the tetralogy of Fallot is discussed. To explain this anomaly, a new theory of transposition is presented. The Eisenmenger complex is produced by an abnormality in the formation of bulbar ridge 3B. Instead of this ridge, the reptilian ridge 4B develops. The subsequent absorption of this abnormally formed bulbus proceeds in an abnormal fashion, causing both the aorta and pulmonary artery to arise from the right ventricle, as in our case, or producing a riding aorta with a septal defect, or a mild form of transposition with an aneurysm of the membranous septum.

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calculation, were expressed in terms of capillaries per square centimeter. Corn plasters were then placed over the marks to protect them. At 4 P.M. of the same day the subjects returned to the laboratory and the capillaries in two of the four areas were again counted. At 9 A.M. the following day counts were made in the same two areas as on the previous afternoon; histamine was then pricked into the skin near all four of the marked areas, and counts were made again. If, for any reason, the ink markings on the skin showed any blurring, as from rubbing or washing by the subject, counts from that area were discarded.

Patients with hypertension\* were selected from the wards and dispensaries of the University Hospital and from the private practices of the authors. As a further control, other patients without hypertension, but of about the same age, were chosen from the same wards and dispensaries and examined similarly. Most of these patients had some form of cardiovascular disease or diabetes, and might be designated "abnormal" controls, as contrasted with the normal controls previously described. Many of the dispensary patients had been in the hospital only an hour when the studies were made. Sometimes the die was used and counts made by the same technique employed for the normal controls. More often the inked circle was omitted, and an entire microscopic field observed. This, roughly, equalled about four of the marked circles. Under such circumstances the absolute figures are only approximate, but the percentage of increase may be estimated with fair accuracy. Although this modification saved time and histamine pricks, after much experience it became clear that the more exact method, using the die, is preferable.

## RESULTS

A. On the normal controls. The absolute figures for capillaries per square centimeter show considerable variation. The number which were open initially ranged from 100 to 1,300 per square centimeter, but most of the figures lay between 200 and 600, as shown in Fig. 1A. Counts per square centimeter after the injection of histamine varied from 250 to 1,300 and showed a little more spread, but for the most part ranged between 500 and 900, as shown in Fig. 1B. There was no significant variation with sex or age, although it should be noted that the young adult and middle-aged subjects predominated in this series. Fig. 1C and 1D show that, as a rule, more capillaries were open at the end than at the beginning of the twenty-four-hour period of observation. This may have been caused by slight irritation from the corn plasters, although we could find nothing less irritating to the skin. The number of subjects with more capillaries open on the second morning was to the number with more capillaries open on the first morning as 4 is to 3; the number of subjects with more capillaries open on the first afternoon was to the number with more open on the first morning as a little more than 3 is to 1.

Fig. 2A shows the difference in counts on the same person in different areas on the forearm, with the highest count plotted against the lowest. The average difference was 224 capillaries per square centimeter, and

\*The patients with hypertension with whom the seven papers of this series deal did not have nephritis, at least in the usual meaning of the term, unless so stated specifically. Certain of the observations reported in Part III were made on patients who did have terminal azotemia.

the range, from 40 to 600. Fig. 2B shows the same difference after the injection of histamine; the range was from 20 to 620, and the average, 220.

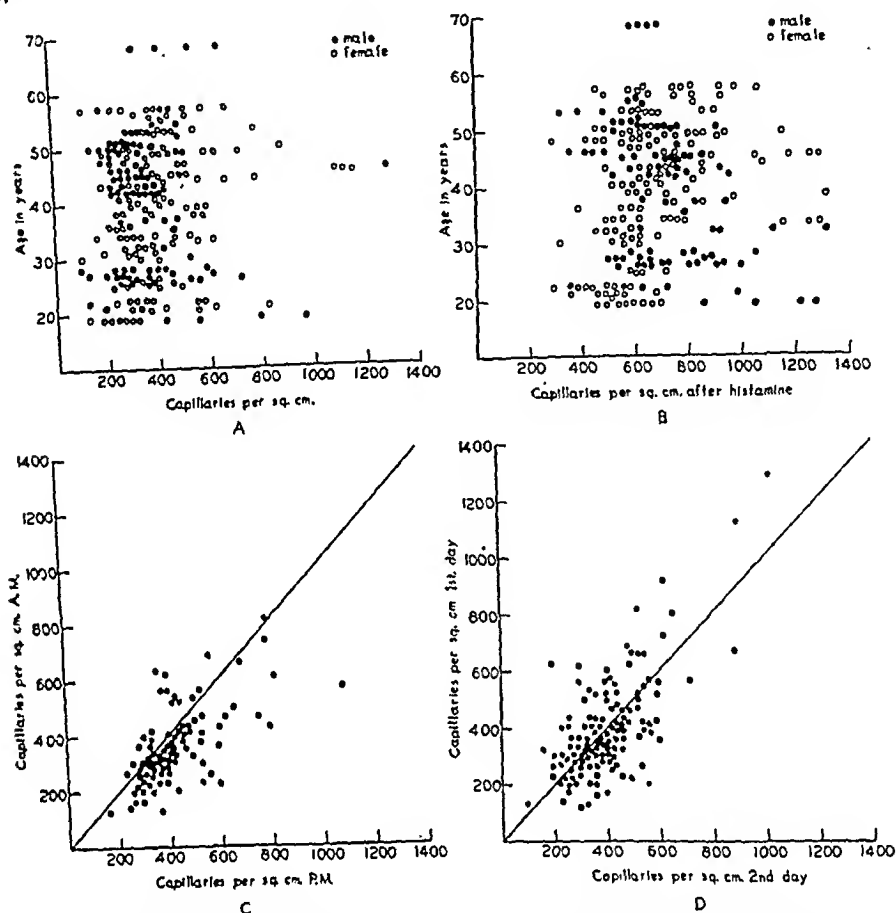


Fig. 1.—A, Capillary counts on normal men and women of varying ages. B, Capillary counts on normal men and women of varying ages, made in areas included in a histamine flare. The persons and the areas counted are the same as in A. C, Capillary counts on the same areas, made in the morning and again late in the afternoon, on normal men and women. D, Capillary counts on the same areas, made on two successive mornings on normal men and women.

Fig. 2C compares the number of capillaries open before the injection of histamine with the number open after giving histamine, in actual figures per square centimeter. If the number open after injecting histamine be taken as 100 per cent, an average of almost exactly 50 per cent were open before giving histamine, although the range was from 20 to 90. In two-thirds of the areas counted, 51 per cent, or more, of the total number of capillaries were open before giving histamine, and in only one-third 50 per cent, or less, before giving histamine. However, in three-fourths of the areas counted, 40 to 70 per cent of the capillaries were open before injecting histamine, and the remaining fourth was divided almost equally between areas with 70 to 90 per cent, and areas with 20 to 40 per cent, of their total number of

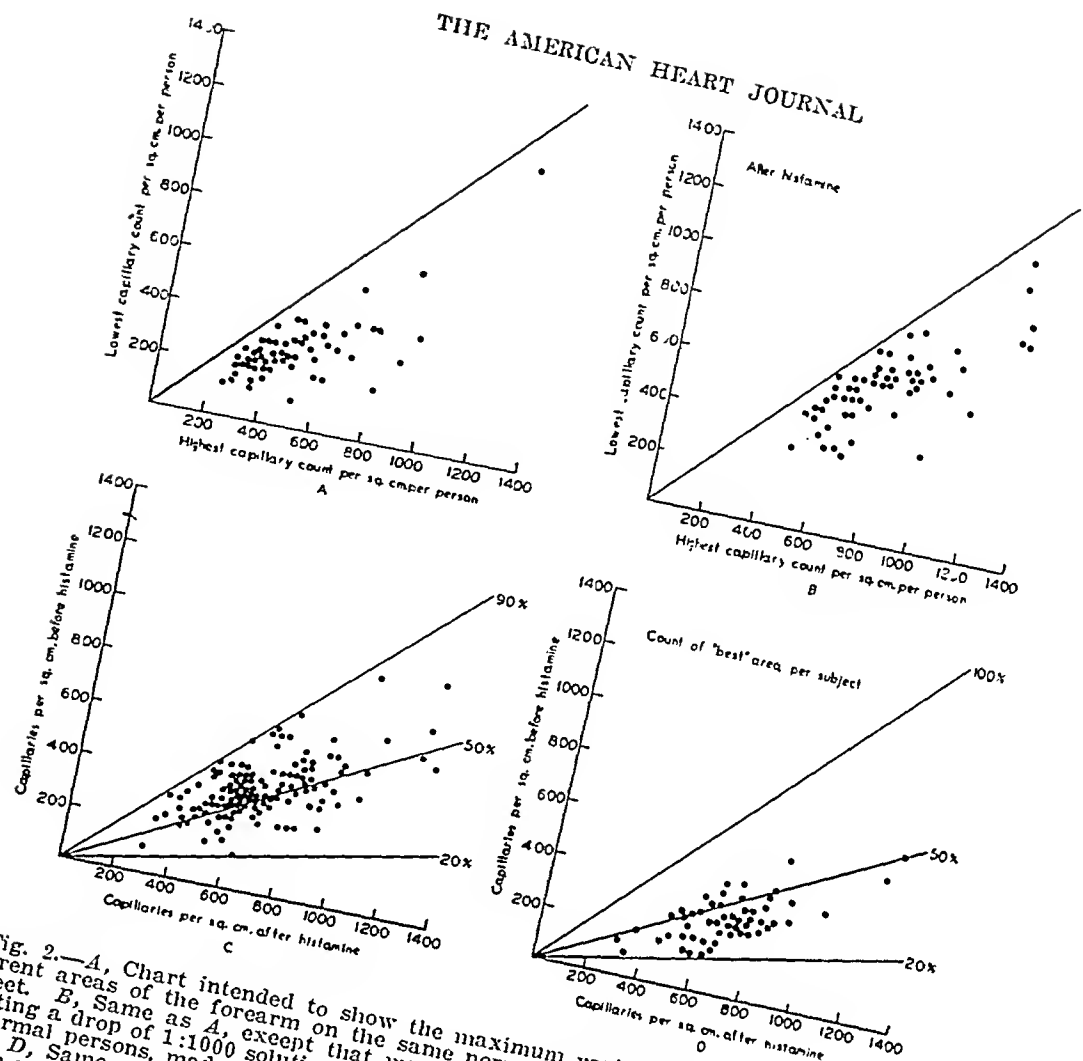


Fig. 2.—A, Chart intended to show the maximum variation in capillary counts on different areas of the forearm on the same normal subject. Each dot represents one subject. B, Same as A, except that maximal local dilatation had been produced by injecting a drop of 1:1000 solution of histamine. C, Capillary counts on the same areas on normal persons, made before and after injecting histamine locally. For details, see text. D, Same as C, except that only one area per subject is charted, and the area chosen was that one of the four in which the smallest per cent of the total number of capillaries were open before histamine. For details, see text.

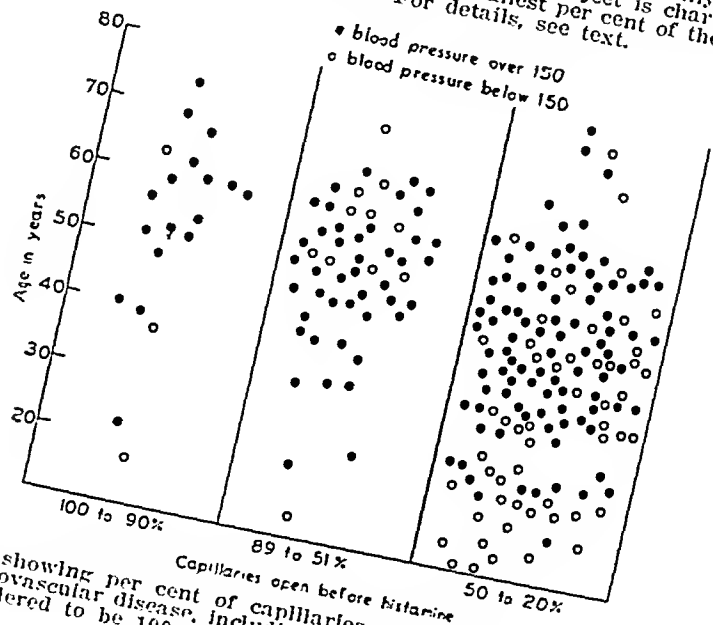


Fig. 3.—Chart showing per cent of capillaries open before injecting histamine in persons with cardiovascular disease, including hypertension. The count after injecting histamine is considered to be 100 per cent. For details, see text.

capillaries initially open. The results are charted somewhat differently in Fig. 2D, in which only one area per person is graphed, and that is the area which had the lowest per cent of total number of capillaries before the injection of histamine. Thus, in this series of normal subjects, every person had at least one count that showed that not more than 62 per cent of the total number of capillaries were open, and four-fifths of the subjects had at least one count below 50 per cent.

B. On patients. Some had hypertension and others did not. The non-hypertensive patients usually had, as previously stated, some form of cardiovascular disease or diabetes, and were not considered normal. Fig. 3 shows the results of studies on 221 such persons, including 156 hypertensive and sixty-five nonhypertensive subjects. Arbitrary divisions were made as follows: (1) Those with 90 to 100 per cent of their capillaries open before the injection of histamine were considered to have diminished capillary mobility. (2) Those with 51 to 89 per cent of their capillaries open before the injection of histamine were considered to have moderate capillary mobility. (3) Those with 50 per cent, or less, of their capillaries open before the injection of histamine were considered to have high capillary mobility. The group with diminished capillary mobility was regarded as definitely abnormal, whereas that with high capillary mobility was considered normal. The middle group, with moderate capillary mobility, was regarded as uncertain; it included some persons who were normal and others who were probably abnormal. It will be seen that 146 subjects fell within the third group, of which ninety-four had hypertension and fifty-two did not. Twenty were included in the first group, which was definitely abnormal; only three of these patients did not have hypertension. The remaining fifty-five, of whom eleven did not have hypertension, fell in the intermediate group. There was no definite relationship between age and grouping.

#### DISCUSSION

Organic capillary changes of a degenerative sort are difficult, if not impossible, to diagnose with methods now available. Even "acute capillaritis," characterized by capillary hemorrhages or "sticking" of leucocytes, is difficult to recognize on histologic section. That some organic change did exist in certain of the cases just reported might be conjectured, at least in the group with diminished, and perhaps some with moderate, capillary mobility. Direct evidence is, however, lacking.

It is probable that many persons with diminished capillary mobility have, in addition, an absolute diminution in number of capillaries. Not enough data have been collected to make this a certainty, but it was more difficult to find fields which were "suitable for observation" in these patients than in normal subjects. The areas which were finally selected for study were chosen only after examining several fields and were

probably above the average in vascularity. The significance of this was not recognized until the study was nearly completed.

It may be difficult or impossible, in certain cases, to differentiate between diminished or moderate capillary mobility and an initial vascular dilatation, such as that which occurs after exposure to sun and wind, in hyperthyroidism, with fever, and in certain skin diseases. The percentile changes may be similar, but other factors aid in differentiation: (1a) If there is initial vascular dilatation caused by exposure to sun and weather, a history of such exposure should be obtainable. The arm may appear weather-beaten. The total count, both before and after giving histamine, is within the normal or high normal range. Branches of the subpapillary venous plexus are usually visible. (1b) By contrast, if the condition is the result of diminished capillary mobility, there is no history of exposure, the arm appears pale, the total count is usually a low normal or below normal, and few, if any, branches of the subpapillary venous plexus are visible. (2) With systemic conditions which lead to vascular dilatation, as hyperthyroidism or fever, there is evidence of the underlying condition. (3) The presence of a skin disease is usually obvious.

Theoretically, an area which is subject to even less exposure than the forearm might be preferred. The upper arm could be used, but this would be much less convenient and open to many of the same objections as the use of the forearm. The face is an exposed area like the hand, and, moreover, the subpapillary venous plexus is always large and dilated, thus interfering with observation of the capillaries. Use of the chest and abdomen is impracticable because respiratory movement makes careful capillary observation impossible. The legs and feet are available, but here the vessels are affected by hydrostatic pressure, and a defective vein could cause more local effects than would systemic disease. We consider the forearm and upper arm the areas most suitable for this type of study.

#### SUMMARY

Capillary counts on the forearm were made on normal persons and on patients with various diseases, especially hypertension. The initial counts were compared with counts made during histamine dilatation; the latter were thought to indicate the total number of capillaries present. It was found that average counts on normal persons showed that 50 per cent of the total number of capillaries were open initially, and, if areas of adequate size were counted, at least one area would show no more than 62 per cent open initially. In certain pathologic vascular states, the initial counts approached or equalled the total counts. After persons with a local or systemic cause for initial dilatation were excluded, the capillary mobility of the remainder was graded as follows: (1) 50 per cent, or less, of total capillaries open initially, high capillary mobility;

(2) 51 to 89 per cent of capillaries open initially, moderate capillary mobility; (3) 90 to 100 per cent of capillaries open initially, diminished capillary mobility. Although most of the persons with hypertension fell into the first, or normal, group, approximately 40 per cent were found to belong in the groups in which there was diminished or moderate capillary mobility. None of the normal controls fell into the group in which mobility was diminished, and, if adequate areas were counted, four-fifths of them showed high capillary mobility.

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# STUDIES OF CRITERIA FOR CLASSIFICATION OF ARTERIAL HYPERTENSION

## II. MINUTE VESSEL PRESSURE

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NUMEROUS methods have been devised for measuring pressure in cutaneous capillaries. The subject has been reviewed by Eichna and Bordley.<sup>1</sup> Indirect methods, such as those described by Danzer and Hooker,<sup>2</sup> and by Kylin,<sup>3</sup> can be used clinically, but the results obtained are unreliable. On the other hand, the direct method of Landis,<sup>4</sup> while admittedly accurate, presents such technical difficulties as to virtually preclude its clinical use. With Landis'<sup>4</sup> method, the pressure is measured without interrupting capillary flow. It should be noted that the indirect methods produce capillary block, with cessation of flow. The method employed in these studies was an indirect one that has been evolved during the past ten years from the Danzer-Hooker method.

### DESCRIPTION OF THE APPARATUS

The apparatus is composed essentially of the following parts:

1. A microscope with Ultrapak attachment and objective for capillary observation.

2. A compression chamber, transparent through the center, with appropriate attachments for exerting a measured pressure on the skin surface.

The following description should be read with the help of Fig. 1.

An ordinary microscope (*A*), with stage detached, may be used. The usual objective-changing device, with the objectives, is removed, and replaced by an Ultrapak (*B*), with special Ultrapak objective (65 X Leitz-Wetzlar). A 10 X ocular of the ordinary type may be used. The Ultrapak is connected (*C*) to the house current through a rheostat, which must be adapted to the type of current available. The microscope is focused in the usual manner.

The compression chamber (*E*) consists of an upper and lower part. The upper part is made of metal, and supports a central disc of optical glass (*D*). One margin is pierced by a metallic tube which connects the chamber with the oil system. At an opposite point on the margin, an outflow screw (not shown), when loosened, permits air and oil to escape and is useful in getting rid of bubbles when the chamber is being filled. The lower part of the compression chamber (*E*) consists of a metal ring which supports a cellophane membrane (*F*). The compression chamber is held on a rod support (*H*) which is moved by a micromanipulator (*I*) (indicated, but not shown). The metal tube leading from chamber *E* is connected by koroseal tubing to a three-way stopcock (*K*). Koroseal is nearly as flexible as rubber and does not rot when left in contact with oil. The three-way stopcock connects with a reservoir for oil (*L*) and a glass side arm (*M*). This side arm (*M*)

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†Obtained from the Merit Products Co., 111 N. Canal St., Chicago, Ill.

is connected by ordinary rubber tubing (*R*) and a Y-tube (*N*) with a mercury manometer (*O*) and a rubber bulb (*P*) which can be compressed by turning a thumb screw in box *Q*.

#### DESCRIPTION OF THE METHOD

Reservoir *L* is partly filled with mineral oil, with stopcock *K* in a neutral position. The escape screw on the upper margin of the compression chamber (*E*) is then loosened, and the chamber tilted slightly so that the screw is uppermost. Stopcock *K* is then turned so that the reservoir is connected only with the compression chamber (*E*), and oil is permitted to flow until all of the air has been expelled from the chamber, after which the chamber is closed by tightening the escape screw. If necessary, more oil may be added to the reservoir (*L*). Then stopcock *K* is turned so that reservoir *L* is connected with the side arm (*M*), and an interval allowed for the oil to rise in the side arm (*M*) to the same level as in the reservoir. Stopcock *K* is then turned as illustrated in Fig. 1, with the chamber (*E*) connected with the pressure system (*OPQ*) and the reservoir disconnected.

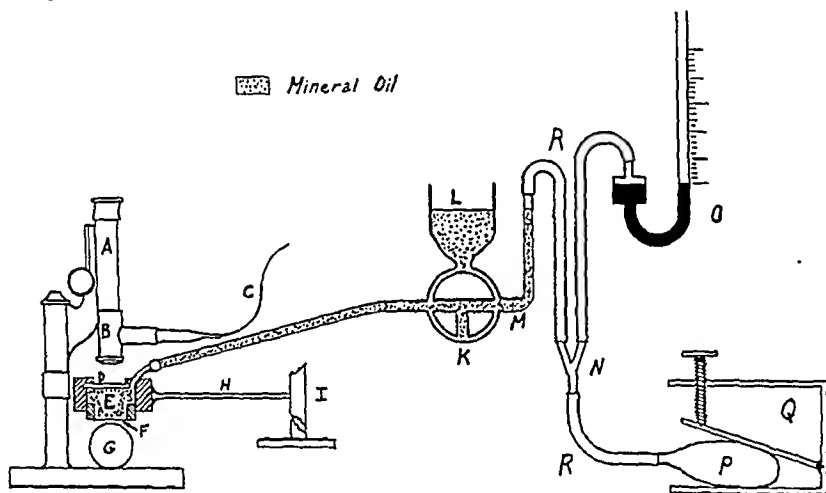


Fig. 1.—Diagram of apparatus for measuring minute vessel pressure. For details, see text.

The measurement is made with the subject seated beside a table, on which the apparatus is placed. When the arm is in position, the area selected for observation is about at the level of the middle of the sternum. An area on the extensor surface of the forearm, a few inches below the elbow, is chosen. The flexor surface may be used, but is less desirable because the greater prominence of its subapillary venous plexus makes capillary observation more difficult. Excessively long hair may be removed by scissors or clippers, but the skin surface must not be scraped. The area to be studied is sometimes marked in ink with a die. The skin is moistened with mineral oil, and the arm is placed in position under the microscope. The position of the arm is indicated (*G*) in Fig. 1.

The chamber (*E*) is lowered by the micromanipulator (*I*) until the cellophane membrane (*F*) makes contact with the skin surface, but without exerting any appreciable pressure on it. In Fig. 1, for greater ease in illustration, the chamber (*E*) appears larger than it need be in relation to the size of the arm. The cellophane membrane may be no more than 1.5 inches in diameter. The capillaries are then visualized through the microscope and watched continuously while the thumb screw on box *Q* is turned, compressing bulb *P*, and raising the pressure in chamber *E*, as shown on manometer *O*. When the capillaries disappear, the manometer reading is recorded.



*Special Precautions.*—1. The cellophane membrane. The attachment of the cellophane membrane to its holder must be loose enough to allow it to bulge slightly downward when the pressure in the chamber is raised. This bulge must be sufficient to permit pressure in the chamber (*E*) to be transmitted to the skin. If the membrane is too tight, or if the pressure measurement is begun with the membrane too far from the skin, the capillaries will not disappear, regardless of the amount of pressure applied. Conversely, if the chamber is lowered too far the cellophane itself will make pressure on the skin, which may obliterate capillaries even before the pressure in the chamber is raised. Making this adjustment requires some experience, but, in general, if the capillaries are readily visible before the measurement and disappear at a certain point when pressure is raised, one may feel confident that the height of the chamber was correct.

2. Oil leakage. Some leakage of oil always occurs around, and possibly through, the cellophane. Therefore, during the course of the measurement, the level of the oil in the side arm (*M*) falls somewhat, and the loss must be made up by connecting with the reservoir before the next determination. The oil level in the side arm (*M*) should never be permitted to fall to the level of the stopcock; if it does, air bubbles will get into the oil system. If they reach the korosol tube or even the chamber (*E*), they should be expelled by opening the escape screw in chamber *E* and letting the oil run through from the reservoir.

*Test of the Method.*—As a rule, readings can be duplicated by the same observer within 2 mm. of mercury, and by two observers within 3 mm. of mercury. However, such duplication does not bear directly upon the question of the accuracy of the method. Theoretically, raising venous pressure should raise capillary pressure. Venous pressure can be raised by inflating a blood pressure cuff about the arm. After a period of adjustment, venous pressure should equal cuff pressure. Eielma and Bordley<sup>1</sup> were unable to obtain graded rises in capillary pressure, as measured by the Danzer-Hooker method, to correspond with increments of cuff pressure. When they used the method of Landis, corresponding rises of capillary pressure were obtained. They concluded that the Danzer-Hooker method was unreliable. The cuff they used was of the usual type which is employed for measuring arterial pressure.

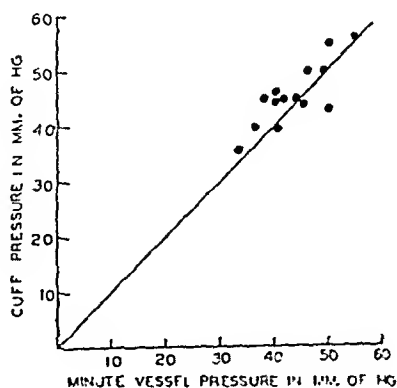


Fig. 2.—Chart intended to show the correlation between artificially elevated venous pressure, produced by inflating a blood pressure cuff about the upper arm, and minute vessel pressure. In every instance the initial minute vessel pressure was 22 mm. of mercury, or lower. For details, see text.

On fifteen different persons, all with initial minute vessel pressures below 22 mm. of mercury, the following procedure was used. One person placed an extra large (5.5 × 20 inches) blood pressure cuff about the upper arm of the subject and inflated it to a pressure unknown to the person reading the minute vessel pressure, which was measured in the usual way on the forearm. In two to four minutes, or

after the minute vessel pressure became constant, the reading was taken, and the results were charted (Fig. 2). Repeated observations on the same subject were considered unwise because of the hyperemia and edema which made it difficult to distinguish capillaries from branches of the subpapillary venous plexus. It will be seen that the minute vessel pressure rose to approximately the same level as the venous pressure. It did not regularly exceed venous pressure, as was the case when it was measured by Landis<sup>1</sup> and Eichm and Bordley<sup>1</sup> by the method of Landis.<sup>4</sup>

*Comparison With the Method of Danzer and Hooker.*<sup>2-1</sup> The forearm is used instead of the finger because (a), as was shown in Part I, changes in the number of open capillaries may occur in the forearm, but not in the hand or finger. The forearm might therefore be expected to reflect systemic changes better, whereas the hand responds maximally to local conditions. (b) The arteriolar and venous limbs of the capillaries pass at right angles to the surface in the forearm, but run parallel to it in the nail bed. Therefore, when pressure is applied to them in the forearm, they empty, but in the nail bed they usually do not.

2. The chamber is maneuvered with a micromanipulator.
3. The chamber is filled with mineral oil instead of air, to improve visibility.
4. A microscope with Ultrapak attachment is used.
5. The end point is disappearance of capillaries. Flow is not observed.
6. The pressure measured is thought to be minute vessel pressure, not capillary pressure. Reasons for this will be discussed later.

*Clinical Material.*—Patients with and without hypertension were chosen from the wards and dispensaries of the hospital of the University of Pennsylvania. Minute vessel pressure was measured by the method just described. Histamine (1:1,000 solution) was then injected into the adjacent skin, and, when the flare area included the area under observation, the measurement was repeated. Many of the same patients from whom data were obtained for Fig. 3 of Part I were studied.

## RESULTS

Minute vessel pressure is plotted against systolic blood pressure in Fig. 3A, and against diastolic blood pressure in Fig. 3B. Each dot represents a measurement on a different subject. The patients were unselected, except that persons with skin rashes and other local cutaneous lesions were excluded. It will be seen that minute vessel pressure never exceeded 25 mm. of mercury until systolic pressure rose above 140, and diastolic pressure above 90. No considerable number of subjects had minute vessel pressures above 25 until the systolic blood pressure exceeded 160, and the diastolic pressure, 100. Above these levels, some hypertensive patients had elevated minute vessel pressures and some did not. However, in the few cases in which the systolic blood pressure was above 250 and the diastolic above 150, minute vessel pressure was uniformly elevated.

As a rule, histamine causes a change in minute vessel pressure. In Fig. 4, such changes are plotted against per cent changes in capillary count. As many of the capillary counts were only approximate, there is a tendency toward clustering near the round numbers. A minute vessel pressure change of 3 mm., or less, was considered within the limit of error of the method, and, therefore, as insignificant. Capillary counts were grouped according to whether the mobility was diminished,

GOOD  
 STAMMARD  
 LEXINGTON, KY.

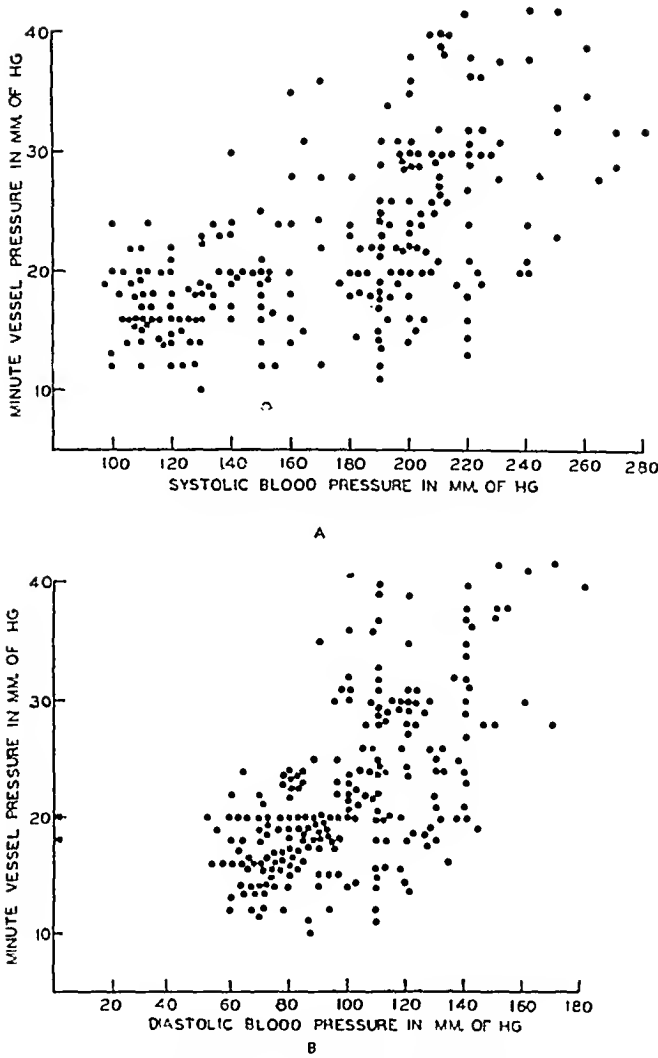


Fig. 3.—A, Chart showing relation of minute vessel pressure to systolic blood pressure. B, Chart showing relation of minute vessel pressure to diastolic blood pressure.

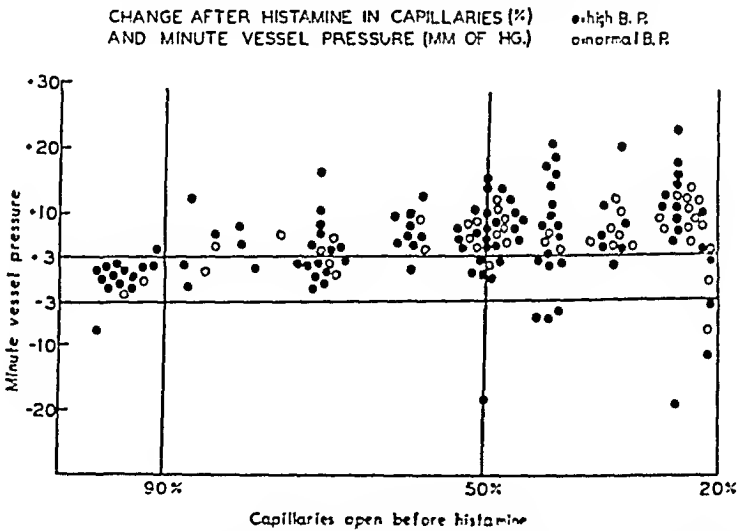


Fig. 4.—Chart showing relation of change in minute vessel pressure after the injection of histamine to "capillary mobility," as defined in Part I. For details, see text.

moderate, or high, as described in Part I. It is apparent that sixteen persons had diminished capillary mobility, and that fourteen of these showed no significant change in minute vessel pressure. Certain persons with moderate and high capillary mobility also showed no significant change in minute vessel pressure, but the proportion was lower. An increase of 13 mm. of mercury, or more, occurred only in subjects with hypertension. Nine persons showed a significant fall in minute vessel pressure. This is difficult to explain, but all of these patients were among those who were studied during the early part of the investigation. None such have been seen in the past year. It is suggested, therefore, that this apparent fall in pressure represented a technical error.

#### DISCUSSION

It appears that minute vessel pressure, as measured by this method, approximately equals venous pressure when the latter is elevated by means of a cuff. It should be noted, however, that this was true only when the extra large cuff was used. True capillary pressure, as measured by the method of Landis,<sup>4</sup> and as applied by Landis<sup>4</sup> and Eichna and Bordley,<sup>1</sup> rises under similar circumstances to a point 8 mm., or more, above venous or cuff pressure. Therefore, the method satisfies the postulates of Eichna and Bordley in one respect, but not in another: (1) It shows that an elevated minute vessel pressure is quantitatively associated with an elevated venous pressure. (2) The minute vessel pressure tends to equal, but not to exceed, venous pressure.

It may be that figures obtained by the indirect method should be considered of relative, rather than of absolute, significance. Skin elasticity and resistance may interpose a tangible, but fairly constant, factor. Moreover, it is not certain exactly what pressure is being measured. Comparison may be made with the actual figures obtained by Landis.<sup>4</sup> The pressures he obtained in normal subjects were as follows: (1) In the arteriolar limb, an average pressure of 32 mm. of mercury, with a range of 21 to 48; (2) at the summit of the loop, an average pressure of 20 mm., with a range of 15 to 32; (3) in the venous limb, an average pressure of 12 mm., with a range of 6 to 18. Thus, as far as actual figures are concerned, the pressures obtained by the indirect method correspond more nearly with those obtained by Landis at the summit of the loop than in the arteriolar limb. Moreover, by the indirect method, it is the summit of the loop that is observed, and this is where the measurement is made.

Nevertheless, for the following reasons, it appears probable that the pressure actually measured by the indirect method varies with the pressure in the precapillary arteriole. The pressure required to block

a capillary in which blood has been flowing is greater than the normal pressure in that capillary while flow is continuing. As the capillary is blocked, the pressure recorded is that at the nearest unblocked branch on the arterial side, i.e., probably the pressure in the precapillary arteriole. This possibility appears to have been insufficiently recognized by other workers. To take an extreme example as an illustration, if it were possible to block all of the capillaries in the body simultaneously, and if the arterial system were entirely rigid, the pressure required to produce the obstruction would be approximately aortic pressure. The pressure required to block one branch of a Y-branching vessel is not the pressure which is normally present at that point under conditions of flow, but rather the pressure at the fork of the Y where a collateral branch is open.

The pressure required to empty a capillary in which there is no flow is the pressure just in excess of that in the subpapillary venous plexus. This, theoretically, should be somewhat less than that required to block the inflow from the arterial side (i.e., by the difference between the pressure in the subpapillary venules and the subpapillary arterioles). Under such circumstances, one would expect some of the capillaries to disappear at one pressure level, and some at a slightly higher pressure, and the latter would include those capillaries in which flow was present. Actually, a pressure change of less than 1 to 2 mm. is all that is required to obliterate all of the capillaries after the first ones have disappeared. A possible explanation is that the pressure that empties the capillaries also blocks the subpapillary venous plexus, which must be connected with the precapillary arteriolar plexus either through capillaries or arteriovenous anastomoses. Thus, in either case, the actual pressure which is measured is that in the precapillary arteriole; it is certainly not true capillary pressure, and the term "minute vessel pressure" is preferable.

Minute vessel pressure does not exceed 25 mm. of mercury in persons whose arterial blood pressure is normal. Persons with elevated blood pressure can be divided into two groups: (1) those with normal minute vessel pressure, and (2) those with elevated minute vessel pressure. As a rule, after the injection of histamine the pressure rises or remains the same. There is a tendency for persons with diminished capillary mobility to have an insignificant change in minute vessel pressure after histamine is given. It is suggested that in such cases there may be sclerosis of the precapillary arteriole.

In normal persons with high or moderate capillary mobility and without hypertension, minute vessel pressure may rise 3 to 13 mm. of mercury after histamine is given. Under similar conditions, some patients with hypertension will show a rise in minute vessel pressure of more than 13 mm. of mercury. In such cases it is possible that arteriolar spasm may be unusually marked.

## SUMMARY

An indirect method for measuring the pressure in the minute vessels of the skin is described. Although the reading is made by inspecting the capillaries, the pressure measured is probably that in the precapillary arteriole. In normal persons the pressure which is measured in this way does not exceed 25 mm. of mercury and will increase 3 to 13 mm. of mercury in the flare area of a histamine wheal. In persons with hypertension the initial minute vessel pressure may be normal or elevated, and, in the area of a histamine flare, it may fail to change, show a normal rise, or show an exaggerated rise of more than 13 mm. of mercury. When the change is less than 3 mm. of mercury, whether or not the subject has hypertension, it is suggested that sclerosis of the precapillary arteriole is present.

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# STUDIES OF CRITERIA FOR CLASSIFICATION OF ARTERIAL HYPERTENSION

## III. CUTANEOUS LYMPHATIC FLOW

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LANDIS<sup>1, 2</sup> has shown that the rate at which fluid leaves the capillaries varies directly with the pressure in the capillaries and inversely with the colloid osmotic pressure of the plasma. It is probable that, when flow is unobstructed, capillary pressure never gets very high because of the rapid loss of fluid. However, if capillary pressure is raised by obstruction of venous outflow (resulting from defective valves, varicosities, etc.), the loss of fluid from the capillary may not be very great, because, as some fluid is lost, the blood colloids become concentrated, and, locally, the colloid osmotic pressure rises. A pathologic change in the endothelium of the capillaries may make them partially permeable to blood colloids, thus lowering colloid osmotic pressure and increasing fluid loss from the capillaries. It is possible, but has not been proved, that such increased loss of fluid may occur even without loss of protein. Again, when gross edema is present, tissue pressure may be raised sufficiently to interfere with loss of fluid through the capillaries. Part of the fluid that leaves the capillaries is reabsorbed into the capillaries, and the remainder passes into the lymphatic system.

While the processes of fluid interchange are admittedly complex, in general it may be assumed that, in the absence of edema and with unobstructed lymphatic vessels, the rate of lymphatic flow should vary directly with the rate at which fluid leaves the capillaries. To avoid artifacts produced by local hyperemia and muscle movements, the part being tested should be at rest. By means of the method of McMaster,<sup>3, 4</sup> it was decided to measure the rate of cutaneous lymphatic flow in a series of persons, and compare the results with measurements of blood pressure and minute vessel pressure.

### METHOD

The dye used was patent blue; it was prepared by the method of McMaster.<sup>3</sup> An attempt was made to see that the subject did not use his arm strenuously for some time prior to the test, although absolute inactivity was considered undesirable. As a rule, the patient was under observation in the laboratory for a half hour before the test was performed. No previous constriction of the arm was permitted, as by a tourniquet or blood pressure cuff. With the patient seated and the forearm motion-

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less on a table before him, approximately 0.03 c.c. of the patent blue solution was injected intracutaneously in the flexor surface of the forearm. After the injection the blue area so outlined was traced on nonwaterproof cellophane with ink and an ordinary fountain pen. Subsequent tracings were made every five minutes for a period of twenty minutes. Attention was paid, not to the size of the initial area injected, but to its increase in size and the extent of its streamers. The final appearance consisted of (1) a central, homogeneously dark-blue area which sometimes spread during the period of observation; (2) a darkly stained web adjacent to the central blue area; (3) a light-blue streamer or streamers extending upward 0.5 to 10 cm. from the central area. The adjacent, deeply stained web probably represents lymphatic vessels directly injected with the dye, and the light-blue streamers probably represent lymphatic spread. Judgment as to cutaneous lymphatic flow is based upon the extent of the streamers, and a distinction is made between normal and increased lymph flow.

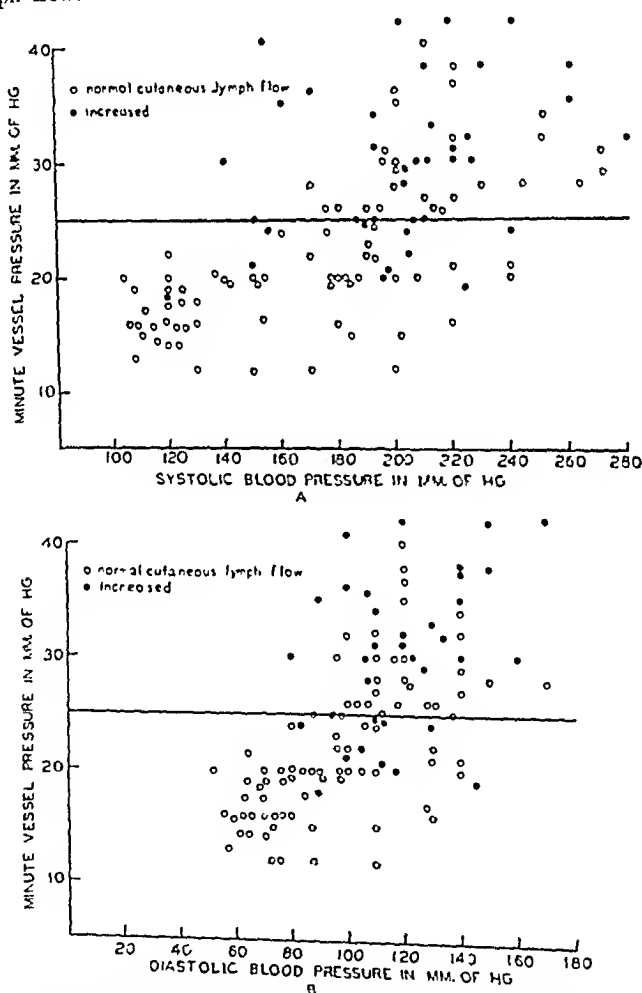


Fig. 1.—A, Chart showing relation between systolic blood pressure, minute vessel pressure, and cutaneous lymph flow in patients, many of whom had cardiovascular disease. B, Chart showing relation between diastolic blood pressure, minute vessel pressure, and cutaneous lymph flow in patients, many of whom had cardiovascular disease.

Minute vessel pressure was measured as described in Part II, and it will be seen (Figs. 1A and B) that many of the same patients were studied again, but this time with reference to their cutaneous lymphatic flow, as well.



A few experiments were carried out on rats in order to clarify certain phases of the relation between minute vessel pressure and cutaneous lymphatic flow. The details of these experiments will be given in Part V; suffice it to say here that if rats are given water by mouth in an amount equivalent to 5 per cent of their body weight, together with an antidiuretic dose of pitressin intraperitoneally, some of them will develop vascular hypertension within 1.5 hours. In Fig. 2 the results of

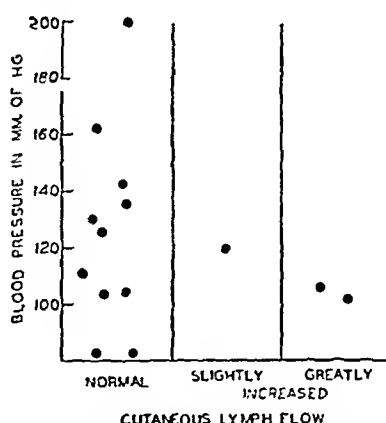


Fig. 2.—Chart showing relation between cutaneous lymph flow and blood pressure in rats which received water by mouth in an amount equivalent to 5 per cent of their body weight, together with an antidiuretic dose of pitressin, intraperitoneally.

measuring cutaneous lymphatic flow and blood pressure in such animals are recorded. Blood pressure was measured by the indirect method of Griffith, and cutaneous lymphatic flow by the patent blue method, in the skin of the lateral abdominal wall. Ether anesthesia was used only when it was necessary to measure the blood pressure and the lymphatic flow.

## RESULTS

It is seen in Figs. 1 *A* and *B* that cutaneous lymphatic flow was increased in thirty-six persons. The minute vessel pressure was below 25 mm. of mercury in eleven of these patients, and above in twenty-five. Of the thirty-six persons, thirty-five had systolic blood pressures of 140, or over, and thirty-four had diastolic pressures of 90, or over. Many persons with equally high or higher blood pressures had a normal cutaneous lymphatic flow. Plasma protein estimations were made in some instances, but not in all, so that we do not have enough data to say whether, in general, the subjects with increased lymphatic flow and low minute vessel pressure did or did not have a normal plasma protein in all cases. The protein content of the plasma in a few such cases was normal.

Fig. 2 shows the results of the rat experiments. Hypertension in these animals under such experimental conditions is associated with an increased blood volume caused by failure to eliminate fluid properly. Since the dosage of pitressin was minimal, not all of the animals showed the antidiuretic effect and hypertension. It was anticipated that the hypertensive animals would have an increased lymphatic flow. In fact, the three animals with increased lymphatic flow had normal blood

pressures, whereas the three with high blood pressures had normal cutaneous lymphatic flow.

#### DISCUSSION

Discussion of certain theoretical relations between minute vessel pressure and cutaneous lymphatic flow will be deferred until after the presentation of data dealing with blood volume, in Part IV. However, at this time two questions will be considered.

If the minute vessel pressure which is measured is actually the pressure in the precapillary arteriole, then it does not differentiate between cases in which an increased vascular pressure extends through to the capillaries and others in which, in spite of an increase in arteriolar pressure, the arteriolar constriction is sufficient to prevent the excess of pressure reaching the capillaries. It is suggested that measuring both minute vessel pressure and cutaneous lymphatic flow makes such a differentiation possible, at least presumptively. A subject with increased cutaneous lymphatic flow and a normal colloid osmotic pressure may be regarded as having at least a slightly elevated capillary pressure. The cause might be local or systemic. If the person has, in addition, vascular hypertension and an elevated minute vessel pressure, it may be considered that the capillary hypertension is a part of the general vascular hypertension. On the other hand, if a subject has high blood pressure and elevated minute vessel pressure, but a normal cutaneous lymphatic flow, it may be that arteriolar constriction has spared the capillaries and tissues from the effects of the elevated arterial pressure.

In a recent study of cutaneous lymphatic flow, by means of patent blue or some other colloidal blue dye, in the excised ear of the rabbit, Parsons and McMaster<sup>5, 6</sup> showed that the rate of lymphatic flow was much greater with a pulsating perfusion pressure than with a constant pressure. They therefore suggested that it was the pulsation of the arteries themselves which, in certain patients with nephritis without arteriosclerosis, caused an increase in cutaneous lymphatic flow. Persons with sclerotic vessels, on the contrary, would have a diminished rate of lymphatic flow. If this explanation were true, one might expect that young persons with aortic regurgitation would have an increased cutaneous lymphatic flow. However, four such patients have been studied, all under 25 years of age, with diastolic pressures of zero, as measured in the usual auscultatory manner, and the flow was normal in every case. In what other way McMaster and Parson's experimental data can be explained is uncertain, but one suggestion might be made. Lymphatic flow is probably a measure of the amount of fluid lost from capillaries. In a rabbit's ear, perfusion fluid might pass either through capillaries or arteriovenous anastomoses; the latter, as Grant<sup>7</sup> has shown, are very numerous in the rabbit's ear. Only fluid which actually passed

through the capillaries would contribute to lymph formation. The pulsating perfusion method is probably the best way to obtain complete capillary injection. McMaster made no direct observations as to the route his perfusion substance was taking. Therefore, perfusion with pulsating pressure might have caused increased lymphatic flow simply because the capillaries were better perfused.

#### SUMMARY

Cutaneous lymphatic flow may be increased or normal in patients with high blood pressure. When increased, it is frequently, but not invariably, associated with increased minute vessel pressure.

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# STUDIES OF CRITERIA FOR CLASSIFICATION OF ARTERIAL HYPERTENSION

## IV. BLOOD VOLUME

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**I**NCREASE in blood volume has not been generally accepted as a possible factor in the development of hypertension. Rowntree, et al.,<sup>1</sup> and Levin<sup>2</sup> found that there was a greater spread of values for blood volume in hypertensive subjects without obvious renal disease than in normal persons, but the averages were about the same. Levin<sup>2</sup> reported a number of cases of hypertension, with associated renal disease, in some of which the blood volume was elevated, and Rowntree, et al.,<sup>1</sup> found that there is a tendency toward high values in nephrosis. If hypertension is indeed an entity, the study of a small series of cases would justify a conclusion. If hypertension is not an entity, it would be necessary to measure the blood volume in every form of hypertension before making a generalization. The results of animal experimentation show that in induced hypertension the blood volume is not necessarily normal. The view will be emphasized that there is a type of hypertension which is associated with, and perhaps secondary to, increased blood volume.

Blood volume has been reported as normal in (1) Goldblatt's form of renal hypertension<sup>3</sup>; (2) the vascular hypertension that follows the intraaortic injection of colloidal kaolin<sup>4</sup>; and (3) the hypertension that follows the repeated injection of pitressin in antidiuretic doses (as described in Part V).

Blood volume has been found to be increased in (1) the hypertension that follows the extravascular injection of 15 c.c. of water or physiologic saline per 100 Gm. of body weight<sup>5</sup>; (2) the hypertension that follows the administration by stomach tube of 5 c.c. of water per 100 Gm. of body weight, together with an antidiuretic dose of pitressin given intraperitoneally (as described in Part V); and (3) the Champlin-Ferris type of renal hypertension.<sup>6</sup>

Blood volume has been found to be low in (1) the hypertension that follows the intravenous injection of adrenalin<sup>7</sup>; (2) the hypertension that soon follows the intraperitoneal injection of pitressin in pressor doses (as described in Part V); and (3) the hypertension that appears a week or more after the intraperitoneal injection of ergotamine tartrate.<sup>8</sup> In addition, the blood volume was found, by Harris and Gibson,<sup>9</sup> to be

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low in glomerulonephritis, frequently when there was an associated hypertension, and low values also occur in eclampsia with hypertension.<sup>10</sup>

It seemed that the subject might be worth reinvestigating. The choice of method required consideration. There are three general types of dye methods: (1) the original method of Rowntree, et al.,<sup>1</sup> later used extensively by Levin<sup>2</sup>; (2) the method of Sunderman and Austin<sup>11</sup>; and (3) the method of Gibson and Evans.<sup>12</sup>

#### METHOD

The method chosen was that of Sunderman and Austin.<sup>11\*</sup> At first, the Congo red recommended by these authors was used; later, Evans blue (T1824), as recommended by Gibson and Evans,<sup>12</sup> was employed.

Results have been variously reported in terms of body weight (Rowntree, et al.,<sup>1</sup> Levin,<sup>2</sup> Sunderman and Austin<sup>11</sup>), surface area (Gibson and Evans<sup>12</sup>), and height (Harris and Gibson<sup>9</sup>). Gibson uses height alone when edema or some other factor might be thought to influence body weight. It was finally decided to express the results in terms of body weight, although surface area might be preferable if the subjects were of definitely abnormal proportions.

#### METHOD

The subjects were taken from the wards and dispensaries of the hospital of the University of Pennsylvania. As a rule, patients with hypertension were chosen, although an occasional patient with normal blood pressure was included as a control. A large series of normal controls was considered unnecessary, in view of the standards for serum volume previously set up by Sunderman and Austin.<sup>11</sup> Although patients with hypertension were chosen somewhat indiscriminately, an attempt was made to include patients with relatively severe hypertension, especially those with papilledema, and to exclude patients with congestive heart failure.

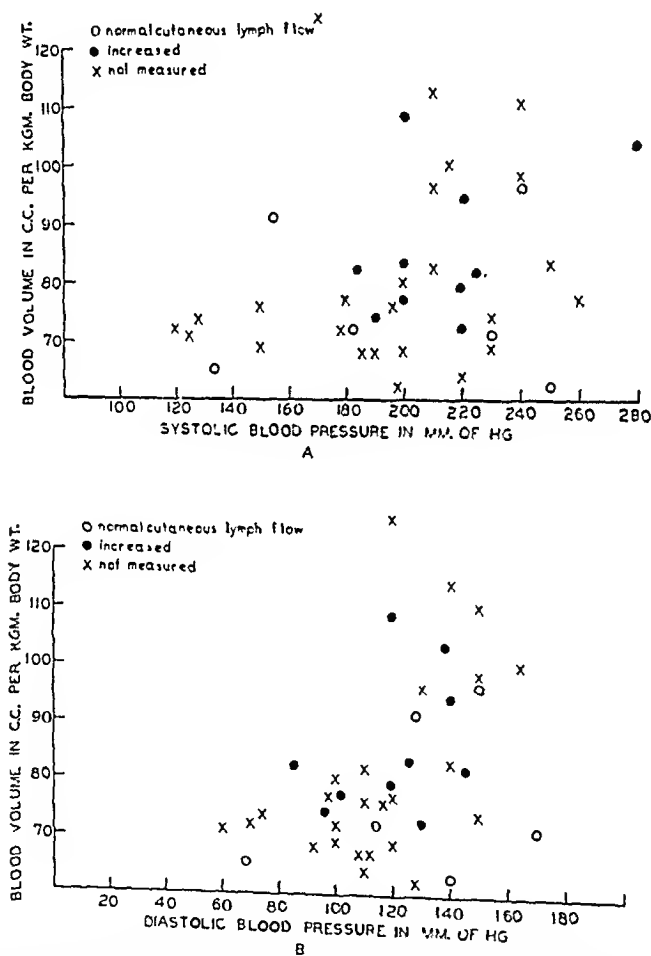
The patient was brought to the laboratory at 9 A.M., without breakfast. Early in the investigation the basic technique of Sunderman and Austin<sup>11</sup> was followed throughout. The vein used for the injection was never utilized for the collection of samples, and usually a vein of the opposite arm was chosen. When the dye was changed to Evans blue, it was found necessary to give only 20 mg., regardless of the patient's weight. This was dissolved in 7 c.c. of distilled water, and, as a rule, samples were taken at the same intervals as when Congo red was used. If it became necessary to reduce the number of venipunctures, one or two samples only were taken. In every case standards were prepared by adding dye from the same ampoule as that used for the injection to appropriate dilutions of the patient's own dye-free serum (i.e., serum obtained before the injection of dye). Hematocrit determinations were made in duplicate, and blood volume was calculated from the serum volume and average hematocrit reading.

Estimations by the Congo red method were made with a Vim Sheftel (visual) colorimeter; the Evans blue values were read in a Klett-Summerson photoelectric colorimeter. The measurements appeared to be comparable in every way, but the blood level of Evans blue tends to remain more constant than that of Congo red, and, therefore, repeated samplings at thirty-minute intervals are less important

\*The authors desire to express their gratitude to Dr. Sunderman for assistance with the first two determinations, and to Dr. Austin for his continued advice.

with the former. As a rule, it made a difference of less than 1 c.e. per kilogram of body weight whether the calculations were made from the thirty-minute, 60-minute, or 90-minute sample, or the average of all three. The differences were not sufficiently great nor uniform to justify extrapolating to 0 time, as recommended by Sunderman and Austin<sup>11</sup> for Congo red.

Some, but not all, of the patients whose blood volume was estimated also had measurements of minute vessel pressure and cutaneous lymphatic flow. These were not made in many cases because the study of blood volume was commenced before the other investigations were begun. Moreover, it was not practicable to make blood volume measurements on all patients on whom the other observations had been made.



1A and B) that eighteen of forty-one estimations showed some increase in blood volume. There was no consistent relation with the degree of hypertension, at least none with systolic pressure (Fig. 1A), but it will be seen that high blood volume was usually associated with a diastolic pressure of more than 120 (Fig. 1B). However, with high diastolic pressures, as well as with high systolic pressures, many persons had normal blood volume.

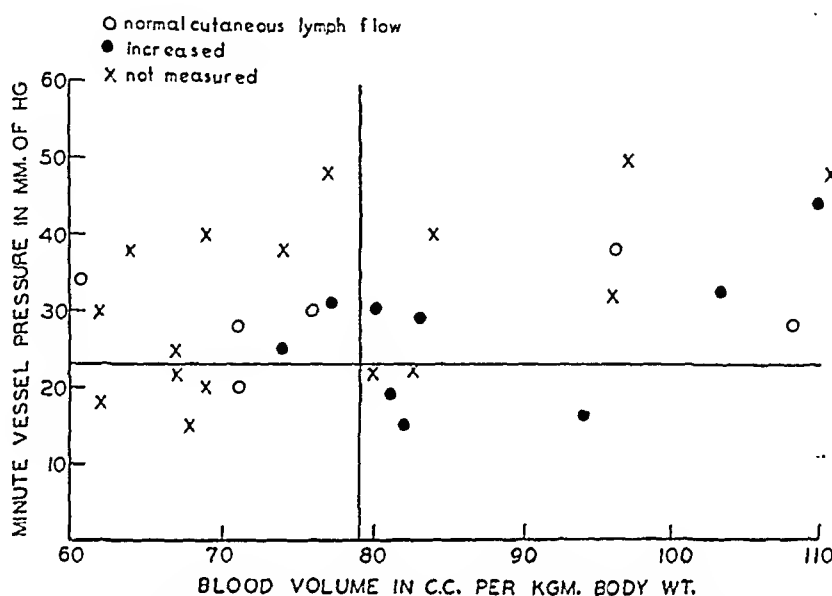


Fig. 2.—Chart showing relation between blood volume, minute vessel pressure, and cutaneous lymph flow. For details, see text.

Measurements of cutaneous lymphatic flow were too few to be conclusive, but no consistent correlation of blood volume with lymphatic flow was evident. However, in Fig. 2, in which blood volume is shown in relation to minute vessel pressure and cutaneous lymphatic flow, there is a suggestion of correlation between high blood volume and increased cutaneous lymphatic flow, and, in the three subjects with increased blood volume and normal minute vessel pressure whose cutaneous lymphatic flow was measured, it was found to be increased.

#### DISCUSSION

*A. Schematic Presentation of the Relations Which We Believe May Be Properly Postulated Between Minute Vessel Pressure, Cutaneous Lymphatic Flow, and Blood Volume.*—The relations between blood volume, minute vessel pressure, and cutaneous lymphatic flow are obviously complex. The following hypothetical schema should be read with reference to Fig. 3.

*General considerations.*—1. Assume that the introduction of water into the blood stream, either from the gastrointestinal tract (*B*) or directly by injection, tends to result in (a) increased urine formation and excretion (*K*), (b) increased blood volume ( $C + M$ ), and (c) in-

creased cutaneous lymphatic flow ( $L$ ). If the amount introduced is not excessive, assume that the only measurable effect will be increased urine elimination ( $K$ ).

2. Excretion of water through the kidney may be interfered with by (a) a deficiency in the number of functioning nephrons ( $H$ ), or (b) increased resorption of water through the tubules ( $J$ ); the latter may perhaps be caused by posterior pituitary hormone. A similar effect may be produced by a deficiency in the blood supply to a normal number of nephrons (reduction in  $E$ ), but under such circumstances we suspect that a pressor substance from ischemic renal tissue may be a complicating factor. Under conditions (a) and (b), assume that blood volume and cutaneous lymphatic flow tend to increase.

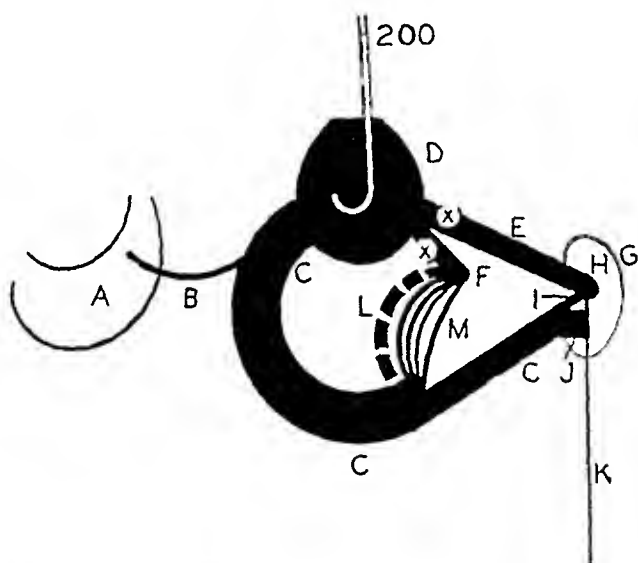


Fig. 3.—Diagram of organs and channels concerned with transfer of water. A, the stomach, representing the gastrointestinal tract; B, water in vessels concerned with absorption from gastrointestinal tract. Water is shown as solidly filled in black areas, as follows: C, in the venous system; D, in the heart; E and F, in the arterial system; H, in the glomerulus; I, in the efferent vessels of the glomerulus; J, in the efferent vessels of the tubules, indicating tubular resorption; K, in the urine; L, in the tissue lymph; M, in the capillaries. G indicates the kidney. Blood pressure (unlettered) is represented by a manometer extending from the heart. It is shown as being elevated, although this is not necessarily the case. For details, see text.

3. Assume that a compensating arteriolar constriction ( $x$ ) may occur in any condition in which cutaneous lymphatic flow tends to increase, and that this may actually prevent such an increase. It may also tend to prevent an increase in blood volume. However, such compensating mechanisms might fail, and arteriolar constriction might be associated with high blood volume and increased cutaneous lymphatic flow. This type of "compensatory" arteriolar constriction should be differentiated from "primary" arteriolar constriction, in which there is no interference with fluid transfer and the arteriolar constriction is the primary cause of the hypertension.

4. Arteriolar constriction tends to be associated with hypertension, and vice versa.



TABLE I

SECONDARY OR ASSOCIATE	PRIMARY VARIATION									
	U		X		+		J		II - OR E - OR II AND E -	
B.V. (C+M)	++	+	++	++	+	+	++	++	++	0
B.P.	0	+	+	+	0	0	+	+	+	+
M.V.P.	0	+	+	+	0	0	0	+	+	+
X	0	+	+	+	0	0	0	+	+	+
II	+	+	+	+	0	0	+	+	+	+
I	+	+	+	+	0	0	+	+	+	+
J	+	+	+	+	0	0	+	+	+	+
K	+	+	+	+	0	0	+	+	+	+
C.L.F. (L)	+	0	+	+	+	+	+	+	+	+

++, greatly increased; +, increased; 0, no change; -, decreased; B.P., blood pressure; M.V.P., minute vessel pressure; C.L.F., cutaneous lymphatic flow. For significance of other letters see Fig. 3.

5. When there is no interruption of flow, capillary pressure can probably never rise very high because any elevation would simply result in increased fluid loss into the tissues, and this would lower capillary pressure. With obstruction on the venous side, however, capillary pressure may be high because early loss of fluid may result in a concentration of plasma protein sufficient to prevent further loss. In general, however, increased cutaneous lymphatic flow (representing fluid lost from the capillaries) would tend to lower minute vessel pressure.

6. Arteriolar constriction interposes resistance to blood flow, so that, as contrasted with the "normal" state, pressure will be high proximal to it and low distal to it. If the zone of constriction includes the precapillary arteriole, minute vessel pressure, as measured by the method described in Part II, will be high. However, if the zone of constriction ends proximal to the precapillary arteriole, minute vessel pressure will not be increased.

Some of the various combinations that may result are listed in the successive columns of Table I, which should be read with reference to Fig. 3. Although the changes of water content in various parts of the renal mechanism are conjectural, it is nevertheless suspected that the combinations suggested in the table have actually been encountered clinically.

*B. Types of Elevated Blood Volume.*—Increases in blood volume may be divided into two major types, metabolic and vascular. By a metabolic increase in blood volume is meant the increase that follows primary increase of water in the blood. This may result from addition of fluid in an excessive amount, or from interference with the normal processes by which it is eliminated. For example, Austin and McGuinness<sup>13</sup> reported the case of a patient who was given a large dose of acacia intravenously, and subsequently developed a marked, but transient, hypertension. In this case the presence of the acacia prevented the normal elimination of fluid. However, the same phenomena should occur, but to a lesser extent, following the intravenous injection of excessive amounts of any solution. Failure of elimination is, in all probability, the cause of the high blood volume which is associated with the hypertension in rats made hypertensive by the Chanutin-Ferris type of kidney operation.<sup>6</sup> This metabolic type of increased blood volume is discussed in Section A, and its possible relations have been indicated.

By a vascular increase in blood volume we mean the increase which must occur whenever, for any reason, there is a decrease in vascular tone. It is postulated that the increase in blood volume is of this vascular type in the following: (1) in experimental hyperthyroidism in rats, as reported by Griffith and Comroe<sup>14</sup>; (2) in clinical hyperthyroidism, as reported by Chang<sup>15</sup> and others; (3) after bilateral lumbar sympathectomy, as reported by Griffith, Comroe, and Zinn<sup>8</sup>; and (4) during the

recovery phase following the general vasoconstriction produced by ergotamine, as reported by Griffith, Comroe, and Zinn.<sup>8</sup>

We assume that, with increased blood volume of the vascular type, hypertension does not occur and minute vessel pressure is not elevated. Cutaneous lymphatic flow would usually be normal, but some increase might be expected if the plasma protein were sufficiently diluted to lower the colloidal osmotic pressure.

The patients whose increased blood volumes are shown in Figs. 1A and B and two others probably had the metabolic variety. However, it is sometimes impossible to be sure which type is present in a particular case. For example, a boy, 14 years old, had recovered from an attack of acute glomerulonephritis. During the attack his blood pressure was 190/110, but at the time his blood volume was measured it had fallen to 140/90. His blood volume was 92 c.c. per kilogram of body weight (not charted). Other studies as described in Parts I, II, and III were not made, as this was one of the earliest cases in the series. The elevated blood volume may have been of the metabolic type and have arisen from a condition that had been present during the acute attack; or, it may have been caused by a generalized vascular relaxation which occurred in the recovery phase, after a period of intense vasoconstriction (vascular type).

Another man was studied upon two occasions. At first, when he was in fairly good condition, his blood pressure and minute vessel pressure were high and his blood volume was normal. Unfortunately, the technique for measuring cutaneous lymphatic flow was not then available. Studies were repeated some six months later, a few weeks before his death. At that time his blood pressure had fallen somewhat, but was still high; his minute vessel pressure was normal; his blood volume was high; and his cutaneous lymphatic flow was greatly increased. It is suggested that a terminal diminution in arteriolar tone permitted the development of a vascular type of increase in blood volume.

*C. Relation Between Blood Volume and Minute Vessels.*—Observation of cutaneous vessels suggests that there are certain interrelations between blood volume and minute vessels. An arteriole and its cluster of capillaries might be regarded as the smallest vascular unit. Under normal circumstances it is probable that, throughout much of the body, every arteriole is open part of the time and closed part of the time. Under certain conditions the relative duration of these phases may change. For example, in polycythemia vera, an increase in blood volume must be accommodated. Therefore, the arterioles may be open more of the time, or even all of the time. The authors have noted that, in polycythemia vera, all of the cutaneous capillaries in the forearm are open, and that no more are visible after the injection of histamine. This would also explain the observations of Roberts and Griffith<sup>16</sup> in cases of hyperthyroidism.

Another way in which more blood could be accommodated in a given vascular bed would be dilatation of vessels that are ordinarily open. Undoubtedly both of these vascular changes occur, although their relative importance is uncertain. However, it may be accepted as probable that arterioles which, by dilating or constricting, can empty or fill peripheral vascular beds (capillaries) exert an effect on blood volume far out of proportion to that produced by changes in their size. This indicates the peculiarly strategic position of the arterioles in the regulation of blood pressure and blood volume. It is frequently implied that the maximal point of resistance on the arterial side of the capillaries lies in the arterioles, and, by comparing the relative size of the arterioles and larger arteries, this implication appears to be justified. However, because of the normal branching of the arterial tree, it appears that the summated cross section of vessels of any caliber normally exceeds the sum of the cross sections of vessels between them and the heart. It is the tremendous expansion of the vascular bed in the capillaries that accounts for the sharp drop in pressure between the arterioles and the capillaries. The importance of the arteriole lies in its ability to shut off this capillary vascular bed. However, under pathologic conditions, it is possible that the arterioles may assume a barrier role, with a total cross-sectional area less than that of proximal, small arteries.

High blood volume is infrequently associated with high blood pressure, certainly less often than might be suggested by the observations here presented. This was the result of our method of selecting cases, and will be referred to again in Parts V and VII.

#### SUMMARY

Blood volume is usually normal in patients with high blood pressure, but in certain instances it is increased. An increase of blood volume in cases of hypertension is always associated with increased minute vessel pressure, or increased cutaneous lymphatic flow, or both. In an attempt to account for this, various theories are discussed.

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# STUDIES OF CRITERIA FOR CLASSIFICATION OF ARTERIAL HYPERTENSION

## V. TYPES OF HYPERTENSION ASSOCIATED WITH THE PRESENCE OF POSTERIOR PITUITARY SUBSTANCE

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### EXPERIMENTAL AND CLINICAL STUDIES

CUSHING<sup>1</sup> focused attention upon the role of the pituitary in hypertension when he described "the posterior lobe hasophilia of eclampsia, of essential hypertension, and of the atheroscleroses and nephropathies of the aged." Further study of the problem has followed four general channels:

1. The effect of the administration, usually by injection, of extracts derived from the pituitary glands of animals to other animals or man.

2. The effect on animals of the vascular changes which result from the administration of such substances (see, for example, Scheps<sup>2</sup>).

3. Attempts to identify substances, presumably derived from the pituitary, in the blood, urine, or cerebrospinal fluid of man or animals. This has led to the development of many biologic tests and to the collection of many more or less discordant data (see, for example, Anselmino and Hoffman<sup>3</sup>; Teel and Reid<sup>4</sup>; Byrom and Wilson<sup>5</sup>; Melville<sup>6</sup>; Jones<sup>7</sup>; Noble, Rinderknecht, and Williams<sup>8</sup>). Attempts have been made to increase the production of pituitary hormone by some physiologic stimulus. For example, Gilman and Goodman<sup>9</sup> deprived rats of water in order to stimulate the secretion of antidiuretic hormone.

4. Attempts to modify the effects of pituitary hormones by the simultaneous administration of extracts of other glands (see, for example, Shapiro<sup>10</sup>), or by deliberately stimulating or depressing other glands, such as the ovary.

In spite of the mass of facts that has been collected, it is difficult to make a diagnosis of a "pituitary" form of hypertension, and, indeed, there is no uniform agreement that such a type actually exists. The difficulties involved in the clinical use of the information available are as follows: (1) Standards based upon histologic study of the pituitary are seldom of any use to the patient who supplied the pituitary. (2) Study of the effects of pituitary extracts upon the experimental animal, especially as concerns hypertension, has been handicapped by failure to recognize and classify various types of hypertension. (3)

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Biologic tests which rely upon elaborate extractions of urine or serum may be falsely positive or negative as a result of changes in the test material which occurred during the extraction. (4) There is no clinical method of confirming biologic tests. The nearest approach to such confirmation occurred in the case reported by Jones<sup>7</sup> and Noble, Rinderknecht, and Williams,<sup>8</sup> in which the biologic tests became less positive as the patient improved. (5) There is the possibility that disturbance of the endocrine balance in either the patient or the test animal may lead to erroneous results.

Preparations derived from the posterior lobe of the pituitary contain a pressor hormone and an antidiuretic hormone. Therefore, one might expect a difference in the hypertensive response of an animal to a pituitary preparation, depending upon the state of hydration of the animal.

The plan, therefore, was (1) to study hypertension produced by pituitary substances in the experimental animal, under varied circumstances, and to try to establish certain objective standards, such as those described in Parts I through IV, which might be used in the clinical recognition of pituitary hypertension; (2) to develop a biologic test on blood instead of urine, and to minimize the effect of artifacts by avoiding extraction; and (3) to follow the effect, in suitable cases, of pituitary irradiation.

#### A. EXPERIMENTAL STUDIES

1. *Effect of Large Doses of Pitressin\* on Blood Pressure (Pressor Effect) and Blood Volume.*—In many preliminary experiments it had been found that rats which were injected with 0.1 pressor unit, or more, per 100 Gm. of body weight developed vascular hypertension, as measured by the indirect method of Griffith.<sup>11</sup> The blood volume of ten normal rats was measured by the dye method of Griffith and Campbell.<sup>12</sup> Several days later, under nembutal anesthesia, each animal was given 5 pressor units of pitressin intraperitoneally. This was considered a large dose, and had repeatedly produced a marked hypertension (200 mm. of mercury, or more) which lasted several hours. Thirty minutes later blood volume was again measured. The results are tabulated in Table I. Normal blood volume varies between 4.0 and 5.3 c.c. per 100 Gm. of body weight. It will be seen that in every case the blood volume had decreased, in nine instances to pathologic levels.

TABLE I

RAT NO.	1	2	3	4	5	6	7	8	9	10
Weight (Gm.)	158	217	170	180	180	170	152	185	180	190
B.V. before P.	5.1	4.9	4.7	4.8	5.3	4.5	4.3	5.6	4.8	4.8
B.V. after P.	3.8	4.3	3.8	2.4*	2.4*	2.6	2.8*	2.3*	2.4*	2.2*

B.V., blood volume; P., pitressin. Blood volume figures are expressed in cubic centimeters per 100 Gm. of body weight.

\*Actual blood volume was somewhat less, but standards were so established that, in the colorimeter, smaller values could not be read accurately.

\*Parke, Davis and Co. Each cubic centimeter contained 20 pressor units.

2. *Effect of Small Doses of Pitressin (Antidiuretic Effect).*—The procedure was approximately as follows: (1) The effect of water: (a) A preliminary blood pressure measurement was made under ether anesthesia. The fact that the pressure was normal was thus established. (b) One or two days later, without anesthesia, the rat was given 5 c.c. of water per 100 Gm. of body weight by stomach tube. It was then placed in a metabolic cage and urine was collected for  $1\frac{1}{2}$  hours. Then a blood pressure measurement was made under ether anesthesia, as before. (2) The effect of pitressin: (a) About a week later a blood pressure measurement was made to be sure that the pressure was normal. (b) A day or two later each rat was given, intraperitoneally, 0.12 c.c. per 100 Gm. of body weight of a solution of pitressin diluted 1:150 with distilled water. (This dosage was suggested by the work of Burn,<sup>13</sup> and corresponds to slightly over 5 milli-units of antidiuretic hormone. It was chosen because in preliminary work with larger doses it was thought that some animals showed direct pressor effects. Walker<sup>14</sup> states that he was unable "to detect the antidiuretic effect of much less than 4 mU per 100 grams" in rats which received 5 c.c. of water per 100 Gm. by stomach tube.) The urine collection and blood pressure measurement were made after the same interval as before. (3) The effect of water and pitressin: (a) After a rest period of a week, another blood pressure measurement was made to be sure that the pressure was normal. (b) A day or two later each rat was given, without anesthesia, 5 c.c. of water per 100 Gm. of body weight by stomach tube, and, intraperitoneally, an injection of pitressin in the same dose as before. Again, urine was collected over a period of  $1\frac{1}{2}$  hours and the blood pressure measured. In sixteen of these animals blood volume, under ether anesthesia, was measured immediately after taking the blood pressure.

Variations from the above procedure were made in some instances, as follows: (1) In the later steps, new animals were substituted for a few animals which were ill or dying; (2) the interval between experiments was sometimes lengthened to suit convenience; (3) changes were purposely introduced in the order of the three experimental procedures. Both male and female rats were used, but recognizably pregnant females were excluded from the series.

The blood pressure measurements which were obtained after the three procedures are charted in Fig. 1A. None of the animals which received water alone in the amounts used in these experiments developed hypertension; the maximal normal blood pressure was taken as 150 mm. of mercury. Of the animals which were given pitressin, one had a blood pressure of 152, but this cannot be considered significantly abnormal. On the other hand, the blood pressure of eleven of thirty-seven animals which received both water and pitressin rose above 150 and ranged to 220.



Fig. 1B shows the relation between the water retained (the difference between the water intake and the urine excretion in 11½ hours per 100 Gm. of body weight) and the blood pressure in animals which were given water with, and without, pitressin. There is a direct correlation, although not a very close one. However, the antidiuretic effect of the pitressin is obvious. Animals which received pitressin alone either passed no urine at all, or only a few drops, and therefore the results in that group are not included in this figure.

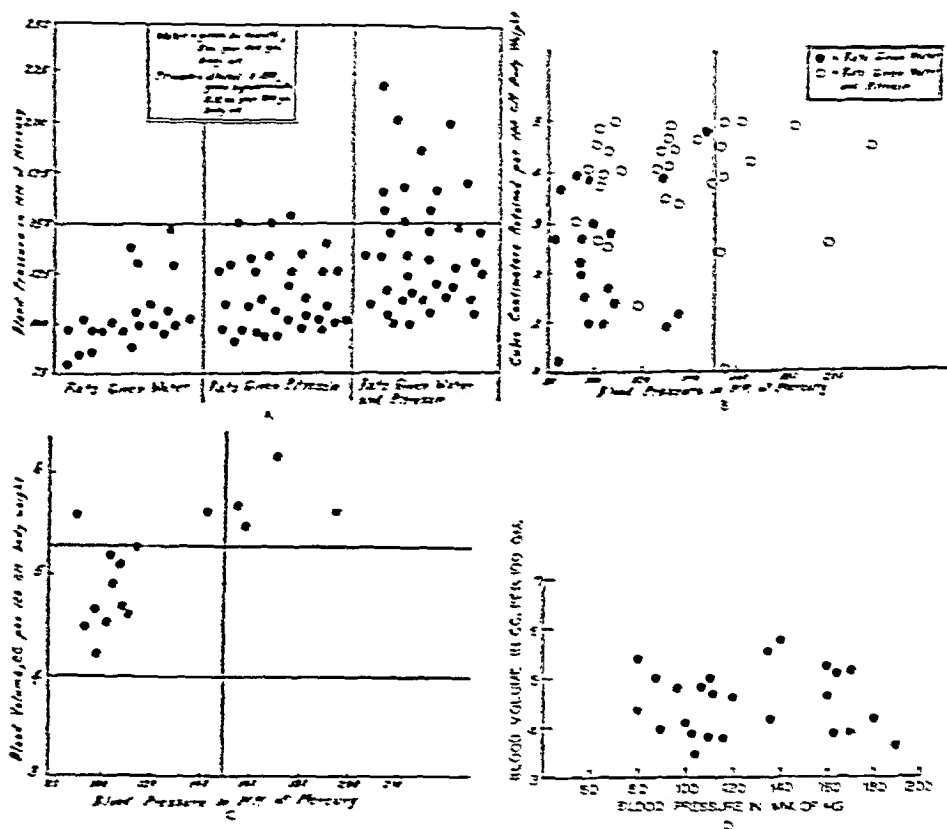


Fig. 1.—A, Chart showing blood pressure measurements of animals which were given either water by mouth, or pitressin by injection, or both. For details, see text. B, Chart showing the correlation between the antidiuretic effect produced by pitressin and the blood pressure level. C, Chart showing the correlation between blood pressure and blood volume in animals which were given both water by mouth and pitressin by injection. D, Chart showing the lack of correlation between blood pressure and blood volume in rats which had been made hypertensive by repeated antidiuretic doses of pitressin.

Fig. 1C shows the correlation between blood volume and blood pressure in sixteen animals that received both water and pitressin. The correlation is direct. One animal in this series had a definitely elevated blood volume with a low normal blood pressure, but in no case did hypertension occur with a normal blood volume. This series should be compared with one previously reported,<sup>25</sup> in which water or physiologic saline was given to rats, either subcutaneously or intraperitoneally, in the amount of 15 c.c. per 100 Gm. of body weight. A certain number of those animals also developed vascular hypertension which was associated with an increase in blood volume, and occasionally an animal had an increased

blood volume with a normal blood pressure. Likewise, in that series, no animal developed hypertension without a high blood volume. It is probable that the mechanism of production of the hypertension in these two series is identical, i.e., 5 c.e. of water per 100 Gm. of body weight by mouth, together with pitressin, would be about equivalent to 15 c.e. per 100 Gm. of body weight by injection, without pitressin.

3. *Effect of Repeated, Small (Antidiuretic) Doses of Pitressin.*—When the experiments of the type described in the previous section were begun, the same animals were used repeatedly, without specific identification. A rest period was allowed between experiments, but no preliminary blood pressure measurements were made. Finally, it was found that all of the procedures appeared to lead to hypertension, and blood pressure measurements which were made on eleven surviving animals showed that seven of them were continuously hypertensive. Therefore, all of the experiments up to this point (fifty-nine) were discarded, and the more carefully controlled procedure described in the previous section was carried out.

We undertook to ascertain whether the persistence of the hypertension was caused by the repeated administration of pitressin, of water, or of the two combined. Therefore, a group of ten rats was selected, five of which were given water and pitressin, and five only pitressin, on seven occasions over a period of nineteen days. The amounts were the same as those used in Series 2. The blood pressure was measured one day, and eight days, after the final injection. On the first day after the final injection, all of the three surviving animals which were given pitressin alone had hypertension; their blood pressures were 195, 185, and 165, as compared with the preinjection measurements of 60, 120, and 95. Four of the five animals which received water and pitressin survived. Their preinjection blood pressures were 85, 90, 105, and 70. On the first day after the final injection, only one animal had hypertension, with a blood pressure of 162, but by the eighth day three animals had hypertension, with blood pressures of 180, 160, and 168. It appeared, therefore, that the pitressin was the cause of the hypertension. The delay in the appearance of the hypertension in animals which were also given water is explained by the condition of the animals. They were given water at such frequent intervals that they developed diarrhea, and, when their blood pressure was measured on the first day after the final injection, they were quite sick, as compared with the animals which received pitressin alone. The three deaths were caused by the respiratory infection which at that time was sweeping through the rat colony.

Subsequently, twenty-five animals were given the same amount of pitressin at approximately the same intervals, and blood pressure and blood volume were measured one day after the final injection. The results are shown in Fig. 1D. Eight of the twenty-five animals were

definitely hypertensive. The blood volume was normal in all. The duration of the hypertension was not definitely ascertained. It lasts, as a rule, eight days or more, and, in one animal, was present (165 mm. of mercury) at the time of the last measurement, which was four weeks after the final injection.

The urea nitrogen content of the blood was measured in nine animals, four of which were hypertensive. It was normal in all cases. The kidneys of ten animals, four of which had been hypertensive, were examined histologically by Dr. Herbert Fox and Dr. James Forrester, of the Pepper Laboratory. No important lesions were found.

#### DISCUSSION

Thus, in experimental "pituitary" hypertension, the blood volume may be low (large dose), normal (repeated small doses), or high (small dose in a hydrated animal). Therefore, one would expect that measurement of blood volume would be of little use in trying to decide whether a particular patient's hypertension was of the "pituitary" type.

The remaining three objective criteria, as described in Parts I to III, will be considered separately:

(1) Change in the number of open capillaries. The cutaneous capillary bed in the rat is quite different from that of man. Moreover, in the rat all studies must be made under anesthesia. The task of establishing normal standards would be enormous. In consequence, such standards are not available, and comparisons with conditions in man are, at present, impossible.

(2) Minute vessel pressure. A technique for measuring minute vessel pressure in the rat is available, and figures have been reported by Griffith and Roberts<sup>16</sup> for normal rats and rats made hypertensive by the intracisternal injection of kaolin. The apparatus described in Part II can be used, but the technique differs considerably from that employed in man. The foot of an anesthetized rat is fixed to a mechanical stage by means of stitches or plasticine, so that the dorsum of the foot is up and somewhat arched. This is the area selected for the observation. The compressing chamber is then lowered until skin contact is made, and the minute vessels are visualized through the microscope. Since these vessels pass parallel to the skin surface, they usually cannot be obliterated by pressure, so that the original Danzer-Hooker end point must be used, i.e., cessation of flow when the pressure in the chamber is raised. For reasons given in Part II, what is measured by this method is pressure in the precapillary arteriole, rather than in the capillary. Complete reliance is not placed on the method for the following reasons: (a) When a blood pressure cuff is placed about the thigh of the rat and the pressure in it is raised somewhat, corresponding increments of minute vessel pressure do not occur (see Part II, test of accuracy of method

in man). As a matter of fact, when pressure is applied to the thigh by the cuff, minute vessel pressure usually falls. This objection may not be valid, however, because of the small size and irritability of the femoral artery of the rat. If the artery is torn, it usually contracts, and little bleeding occurs. It contracts markedly after any manipulation, and it is possible that the cuff about the thigh of the rat affects the femoral artery as well as the vein and thus reduces the arterial inflow; in man the cuff affects mainly the venous return. (b) The rat's foot is thin-skinned, and the bones are very near the surface. Thus, theoretically, the compressing chamber may obliterate vessels larger than capillaries and arterioles. This possibility was suggested when it was found that rats which developed high blood pressure following the intra-cisternal injection of kaolin had elevated minute vessel pressure, whereas it had been anticipated that minute vessel pressure would be normal.

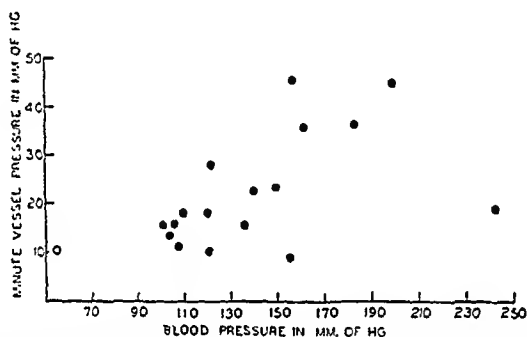


Fig. 2.—Chart showing the correlation between minute vessel pressure and blood pressure in rats which had been injected subcutaneously or intraperitoneally with an amount of water or physiologic saline equivalent to 15 per cent of their body weight.

Therefore, minute vessel pressure was not measured in the present series, but Fig. 2 shows the correlation between minute vessel pressure and arterial pressure in a series of animals which had been made hypertensive by the injection of 15 c.c. of fluid per 100 Gm. of body weight. Although they comprised part of a study made by Griffith, Jeffers, and Lindauer,<sup>17</sup> these particular figures were not reported. For reasons already given, this form of hypertension is thought to be analogous to that produced by smaller amounts of water and antidiuretic doses of pitressin. It is obvious from Fig. 2 that, under experimental conditions, what was supposed to be minute vessel pressure varied directly with blood pressure.

Therefore, judging from Fig. 2, one might suspect that in certain forms of hypertension which are the result of fluid retention, caused perhaps by pituitary hyperactivity, minute vessel pressure might be elevated. This is also in accord with the hypotheses advanced in connection with Fig. 3 and Table I of Part IV, where it was suggested that increased blood volume of the "metabolic" type may be associated with

increased minute vessel pressure. Obviously, the increased blood volume which accompanied the hypertension in Series 3 was of the "metabolic" type.

(3) Cutaneous lymphatic flow. It was shown in Part III that rats which had been given water and pitressin in antidiuretic doses sometimes had an increased cutaneous lymphatic flow, but this occurred in animals that did not develop hypertension. This suggested that, in the experimental animal, arteriolar constriction was adequate to prevent excessive loss of fluid from the capillaries. However, in these acute experiments, water and pitressin were given but once, whereas, in diseased states, one would think of the alteration in the processes of water elimination as acting over an indefinitely long period of time. Under the latter circumstances arteriolar constriction might eventually prove inadequate to prevent loss of fluid from the capillaries, and cutaneous lymphatic flow might be increased. Therefore, one might expect such an increase in certain cases of hypertension caused by pituitary hyperfunction.

Most of what has been said concerns the type of pituitary hypertension characterized by an elevated blood volume. However, other forms, or even transitional forms, may well occur, depending upon the amount, or possibly the character, of the circulating posterior lobe hormone. Therefore, to summarize, in hypertension caused by posterior pituitary hyperactivity (1) the blood volume in the acute stage might be high, low, or normal (in the "recovery" phase it might be normal in the presence of persistent hypertension); (2) minute vessel pressure might be increased; (3) cutaneous lymphatic flow might be normal or increased; (4) papilledema, which, as will be shown in Part VII, occurs frequently in the presence of a metabolic increase in blood volume, might be present; and (5) following a period of pituitary hyperactivity, hypertension might persist even after such activity had subsided. Perhaps during the acute phase certain arteriolar changes occur which require time to regress or may even become permanent. The blood volume should be normal in such cases, and, as the rats during the recovery phase after small doses of pitressin seemed quite well, the clinical condition of the patients should be good. All tests for an excess of posterior lobe substance should be negative. The diagnosis could be made only if the patient had been observed in the preceding period, during which there had been evidence of pituitary hyperactivity.

#### B. CLINICAL STUDIES

*The Biologic Test.*—The test was based on the method of Burn<sup>13</sup> for assaying the antidiuretic content of pituitary substance, and, in the last analysis, is the same as the procedure employed in Series 2 of the animal experiments, except that 1 c.c. of serum was injected instead of the pitressin.

# METHOD

The patient was not prepared in any way. About 10 c.c. of blood was drawn by venipuncture and permitted to clot. The serum was separated, by centrifuging when necessary. As in Series 2 of the animal experiments, rats were given 5 c.c. of water per 100 Gm. of body weight by stomach tube. Passing the stomach tube always caused the animals to empty their bladders. One cubic centimeter of the patient's serum was then injected intraperitoneally, and the animal was placed in a metabolic cage. The volume of urine which was passed at the end of ninety minutes was then measured; complete emptying of the bladder was assured by holding the animal and giving it a few whiffs of ether. The amount of urine voided was subtracted from the amount of water given, and the difference was expressed as cubic centimeters retained per 100 Gm. of body weight. From Fig. 1B it is apparent that normal animals, with rare exceptions, when given water alone, retain less than 4 c.c. per 100 Gm. of body weight, usually considerably less. This fact, together with clinical experience, suggests that retention of 4 c.c., or more, per 100 Gm. of body weight is abnormal. In a few cases the blood pressure was measured under ether anesthesia at the end of the ninety-minute period. Sometimes the degree of dilution of plasma protein was measured by ascertaining the refractometric indices before, and at the end of, the ninety-minute period.

In many instances a simple melanophore expanding test was done simultaneously on the same serum. The technique, based upon suggestions made in Van Dyke's monograph,<sup>18</sup> was as follows: Frogs which had been matched for color were placed in individual containers in "artificial daylight." After a period of thirty minutes or more, when the colors appeared to be constant, the one that was slightly the lighter was injected under the skin of the back with 1 c.c. of patient's serum. The frogs were observed for twenty minutes, and, if the injected frog darkened definitely, as compared with the other, the test was considered positive. This is thought to be a test for hormone from the pars intermedia.

On most of the patients, capillary counts and measurements of minute vessel pressure and cutaneous lymphatic flow were also made; in some cases, blood volume was estimated.

TABLE II  
PATIENTS WITH HYPERTENSION

	ANTI-DIURETIC TEST	
	+	-
Minute vessel pressure normal	2	11
high	21	16
Cutaneous lymphatic flow normal	10	15
increased	12	13
Both minute vessel pressure and cutaneous lymphatic flow normal	0	8
Blood volume normal	2	4
increased	4	5
Papilledema present	8	5
absent	12	18
Melanophore expanding test negative	12	17
positive	3	1*
Sex—male	8	11
female	18	18
Age—range	25-57	17-60
average	40	38
Total	26	29

\*Patient with a pituitary tumor.

## RESULTS

Fig. 3 shows the result of the antidiuretic tests when the sera of normal persons were used. In some cases one rat of the three which were given the subject's serum showed an antidiuretic effect, but never more than one. Figs. 4A and B show the result of similar tests on persons with hypertension. Fig. 4A includes the patients who behaved like normal subjects, and Fig. 4B comprises those whose sera gave an antidiuretic

## ANTIDIURETIC SUBSTANCE ABSENT

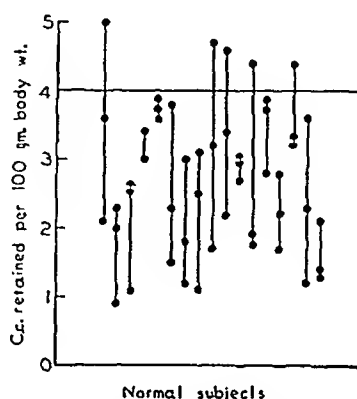
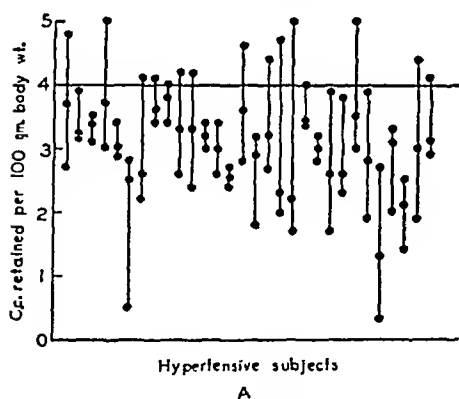


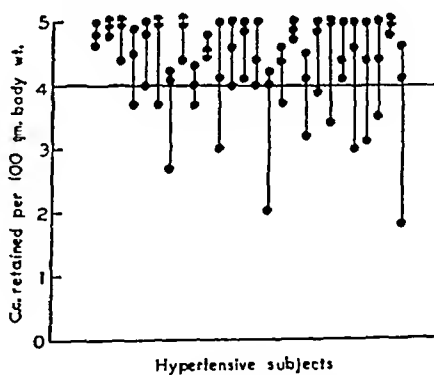
Fig. 3.—Chart showing the amount of water retained over a ninety-minute period, in terms of cubic centimeters per 100 Gm. of body weight. Each animal was given 5 c.c. of water per 100 Gm. of body weight by stomach tube, and 1 c.c. of the serum of a normal person intraperitoneally at the beginning of the test. The three rats used for each subject are indicated by a vertical line joining the dots.

## ANTIDIURETIC SUBSTANCE ABSENT



A

## ANTIDIURETIC SUBSTANCE PRESENT



B

Fig. 4.—A, Same as Fig. 3, except that the sera were obtained from patients with high blood pressure and did not contain an antidiuretic substance for rats. B, Same as Fig. 4A, except that the blood of this group of hypertensive patients did contain an antidiuretic substance for rats.

effect in two or three of the three rats. The characteristic features of the two groups are compared in Table II, but the comparison is not entirely a fair one. It became obvious fairly early in the study that the typical patient with increased posterior pituitary lobe activity (assuming that this is demonstrated by the test) and hypertension had an increased minute vessel pressure and a better than 50 per cent chance of having an increased cutaneous lymphatic flow. Therefore, patients were later selected for study on the basis of these criteria, with the result that these phenomena were observed in many of the patients who had

negative tests. A positive test for melanophore expanding substance seldom occurs, but, when it does, it is perhaps confirmatory. The differences in total figures on certain tests are the result of including a few negroes.

#### DISCUSSION

The presence of an antidiuretic substance in the serum does not necessarily indicate increased activity of the posterior lobe of the pituitary. Walker<sup>14</sup> found such substances in the urine of animals, both under conditions of hydration and dehydration, and after hypophysectomy. However, such a substance could originate in the posterior lobe of the pituitary, and it affects diuresis in the same way as pitressin. The stimulus to posterior lobe secretion in dehydrated animals is not necessarily comparable quantitatively with that which may occur in patients under pathologic conditions. The best evidence to suggest that such an antidiuretic substance is of pituitary origin is the fact that it disappeared after adequate pituitary irradiation in fifteen cases. Although it usually tends to recur, in one case in which there was no hypertension, reported by Edeiken and Griffith,<sup>15</sup> there has been no recurrence over a nine-month period. In one case of hypertension the antidiuretic substance disappeared for six months. During the first two months of this period the systolic blood pressure fell from 200 to 130 and remained low for four months. However, the antidiuretic substance returned, and two weeks later the blood pressure had risen to 180, and a week later to 190. After further irradiation the substance disappeared, and the blood pressure returned to 128. It is too early to evaluate the results in this case. In general, however, the amount of reduction in pressure is likely to be disappointing. Headaches may be relieved at first. Papilledema has disappeared in two cases. The study of the treatment of such patients by irradiation will be continued, and reported with Dr. Pendergrass and Dr. Hodes. At the present time it is mentioned primarily to lend support to the suggestion that the antidiuretic substance in the serum is of pituitary origin.

Positive tests for the antidiuretic substance have been obtained in persons without high blood pressure, and in certain cases in which the existence of true pituitary disease appeared to be unlikely. These include patients with malignant tumors, pregnant women, and one patient with recurring duodenal ulcer. Further study of such cases is in order, but their occurrence suggests that complete acceptance of the test as an indication of posterior pituitary disease must be deferred. However, in those cases in which the test can be changed from positive to negative by pituitary irradiation, the evidence is considerably stronger. Such a test of irradiation has not been employed except in patients with hypertension and women with symptoms presumably caused by fluid retention during menstruation.



Hypertension and plasma protein dilution occur in certain rats that have been injected in the usual manner with serum containing anti-diuretic substance. To measure these changes greatly complicates the test, and it is not certain that thereby one adds to the percentage of true positives. Whether these measurements can be safely omitted is a question that the future must decide. The evidence collected to date suggests that they can be omitted.

The fact that the blood pressure does not fall to normal as the anti-diuretic substance disappears from the serum may be analogous to the persistence of the hypertension after repeated, small injections of pitressin. When the blood pressure does fall, it does so gradually over a period of about two months.

#### SUMMARY

Hypertension in rats was produced by giving a single, large dose of pitressin, a single, small dose of pitressin, together with fluid by mouth, and repeated, small doses of pitressin. In the three forms of hypertension, the blood volume was, respectively, low, high, and normal. A biologic test for an antidiuretic substance in the serum of patients is described. This test was positive in certain cases of high blood pressure. Such patients usually have increased minute vessel pressure, about 50 per cent have increased cutaneous lymphatic flow, and some have papilledema. The blood volume may be normal or increased. In such cases the test may become negative after pituitary irradiation, with, usually, some clinical improvement and a variable effect on blood pressure. The test is not specific for posterior pituitary hyperactivity, but, when it is positive in a particular case, it may serve as a measure of the effect of pituitary irradiation. If it subsequently becomes negative, the inference is that the pituitary was at fault.

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# STUDIES OF CRITERIA FOR CLASSIFICATION OF ARTERIAL HYPERTENSION

## VI. TREATMENT WITH THIOCYANATE

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SINCE Barker's report,<sup>1</sup> in 1936, potassium thiocyanate has been used in the treatment of hypertension in certain cases from the wards and dispensaries of this hospital and the private practices of the authors. Until April 14, 1940, 168 persons had been so treated. The early results have been reported previously.<sup>2</sup> Only 101 of these 168 patients have been followed long enough and have been under sufficiently close observation to estimate the results of the medication. In fifty-nine cases the treatment has been successful, and in forty-two, unsuccessful. The treatment was regarded as successful when the patient maintained a systolic blood pressure of 170, or lower, a diastolic of 110, or lower, and felt subjectively improved, while the blood content of thiocyanate was 8 to 11 mg. per 100 c.c. of serum. Failure meant either that the blood pressure did not fall or that the patient felt worse when it did.

### METHOD

Studies of minute vessels, as outlined in Parts I and II, were made on fifty-eight persons with hypertension who were treated with potassium thiocyanate. The cutaneous lymphatic flow was measured in twenty-eight of these cases. The general procedure and the method of estimating the thiocyanate level in the blood have been previously reported.<sup>2</sup> Blood volume was measured only in cases in which hospitalization was required. In these cases the patients were likely to have more severe symptoms, and be more ill, than those who were treated in the dispensary. Therefore, the blood volume estimations cannot be considered representative of the entire group. The blood volume was measured in only twelve cases. The amount of antidiuretic substance in the blood was measured in a few cases, as described in Part V. Since this test has been developed just recently, it was used in only a few new cases, and in old cases in which thiocyanate had had no effect.

### RESULTS

The results are charted in Fig. 1. From such a small series absolute conclusions cannot be drawn. However, certain trends are apparent. A successful result is obtained more often when the minute vessel pressure is normal than when it is elevated. Furthermore, sclerosis of the precapillary arteriole (defined in Part II as failure of minute vessel pressure to change more than 3 mm. after the injection of histamine) or diminished (occasionally moderate) capillary mobility lessens the

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likelihood of a good response. An increase in cutaneous lymphatic flow is probably even more important in prognosis, for only one of eight responded favorably to thiocyanate, and that one had a normal minute vessel pressure! Unfortunately, the protein content of the plasma in that case was not measured.

Eleven patients who had hypertension with papilledema (choking of one diopter, or more) were treated, without effect either on the blood pressure or the papilledema. This is probably significant.

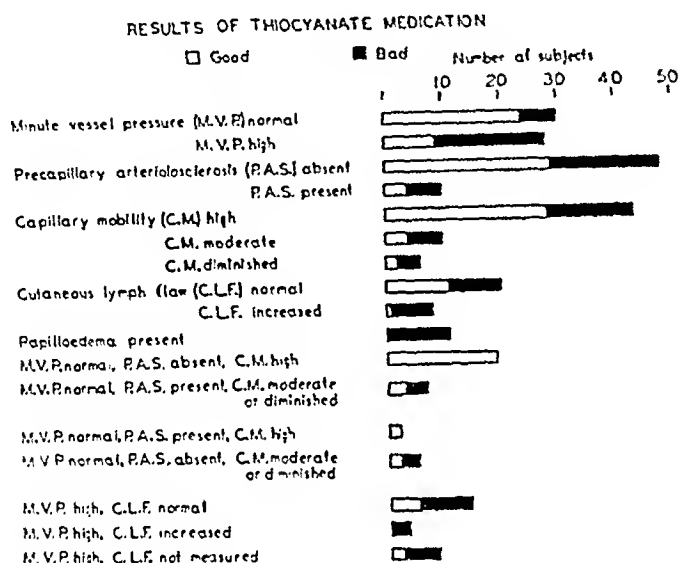


FIG. 1.—For details, see text.

Nineteen persons with normal minute vessel pressure and normal reactions to histamine were treated successfully. The cutaneous lymphatic flow was normal in all of the cases of this group in which it was measured except one, as previously mentioned. The results in this group are probably also significant, but it should be stated that the patients in this group had few or no symptoms in the beginning and, therefore, did not notice the therapeutic success.

In the group in which there was an elevation of minute vessel pressure, or precapillary arteriolar sclerosis, or diminished capillary mobility, or all three, the results were more or less variable. The majority failed to respond to thiocyanate therapy. However, some of the best symptomatic results in the entire group occurred in certain of these patients who did respond with a fall in pressure. On the other hand, five such patients were made definitely worse by the treatment.

Thiocyanate was given to a number of negroes, some of whom responded well, and some did not. As a rule, the tests as outlined cannot be applied to them because of the cutaneous pigmentation. However, capillaries can be visualized occasionally in the negro, and, in a greater number, the spread of patent blue can be followed.

## DISCUSSION

This will deal with (1) toxic effects, (2) effect on symptoms, and (3) relation to the tests and studies described in Parts I to V.

(1) *Toxic Effects*.—True toxic thiocyanate effects of any severity should never occur if the treatment is under proper control. One occasionally observes dermatitis or diarrhea as a manifestation of drug idiosyncrasy. Nausea and vomiting can usually be avoided by giving the drug in dilute solution. A certain degree of lassitude is sometimes noted as the blood pressure starts to fall. Nervousness and a sense of exhaustion occur occasionally when the blood level reaches 13 to 15 mg. per cent. In this study the highest blood level observed was 17 mg. per cent, so that the more marked toxic effects described by Barker<sup>1</sup> and others were not seen.

(2) *Effect on Symptoms*.—In five cases in which the treatment was regarded as a failure, there were symptoms which should perhaps be ascribed to the lowered blood pressure rather than to thiocyanate toxicity. These symptoms occurred when the thiocyanate content of the blood was not above therapeutic levels and coincidentally with the fall in pressure. Such symptoms included faintness, dizziness, syncope, and mental confusion. Possibly these patients had a disproportionate degree of sclerosis of the cerebral vessels. If cerebral vessels were unable to dilate, a high pressure might be required to maintain the cerebral capillary circulation.

Patients with renal insufficiency eliminate thiocyanate more slowly and are likely to require smaller doses. The renal status may change suddenly, and, if the dosage is not properly regulated, complications may ensue. For example, a patient who had been well controlled for 1½ years on a constant dose was hospitalized for cystoscopic study. Catheterization of the left ureter caused some trauma and pain, but no other obvious untoward effects. One day later the patient felt rather weak, and her blood pressure was found to be 120; her usual pressure under treatment had been 150. Her blood thiocyanate level, which one week before had been 10 mg. per cent, was 17 mg. per cent. The dosage had not been changed. Administration of the drug was stopped, and two days later the blood level was still 14 mg. per cent. She recovered, and, eventually, after the usual dose had been resumed, the thiocyanate concentration in her blood returned to its original level. A fatal accident might perhaps have resulted if the administration of the drug had been continued uninterruptedly.

(3) *Relation to Special Tests and Studies*.—If arterial hypertension is not to affect the minute vessels, there must be some increase in the arteriolar barrier, i.e., the arterioles must be narrowed either by spasm or organic change. If the arteriolar contraction is primary, the arterial hypertension is secondary and compensatory, in that it is necessary to maintain the capillary circulation. If general vascular hypertension

(as opposed to mere arterial hypertension) is primary, e.g., as a result of failure to eliminate fluid at the same rate at which it is absorbed, arteriolar constriction might be regarded as compensatory, preventing an excessive increase of pressure in the capillaries and excessive loss of fluid into the tissues.

It is probable that thiocyanate relaxes arteriolar spasm. In partial support of this is the observation that occasionally a patient who responds successfully to thiocyanate may develop an increase in cutaneous lymphatic flow. Therefore, thiocyanate should fail, theoretically, if the narrowing is caused by organic change, or if the spasm is itself compensatory, or if the spasm is too strongly maintained.

The actual observations tend to support this hypothesis. Minute vessel sclerosis is frequently present when the treatment fails. That this is not always the case may mean that the cutaneous vascular area does not always behave like other vascular areas. Arteriolar spasm may be regarded as compensatory if there is an increased cutaneous lymphatic flow with no lowering of serum protein. This agrees with the few observations which are available, and with the experimental data charted in Fig. 2 of Part III. The degree of maintenance of the arteriolar spasm may possibly be estimated from the magnitude of the rise in pressure after administering histamine. In a few cases in which the minute vessel pressure was elevated, histamine produced a further rise of as much as 20 mm. of mercury, as shown in Fig. 4 of Part II. In such cases there was no response to thiocyanate, which may be unable to relax the intense spasm.

#### SUMMARY

The administration of thiocyanate is most likely to be efficacious in the treatment of hypertension if the minute vessel pressure is normal and the capillary count and minute vessel pressure react normally to histamine. Any variation from the normal response to the various tests which we employed makes success less likely. The treatment is least likely to succeed when an elevated minute vessel pressure is associated with increased cutaneous lymph flow, or when papilledema is present.

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# STUDIES OF CRITERIA FOR CLASSIFICATION OF ARTERIAL HYPERTENSION

## VII. INCREASED INTRACRANIAL PRESSURE AND PAPILLEDEMA

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NUMEROUS writers, including Shelburne, Blain, and O'Hara,<sup>1</sup> Masserman,<sup>2</sup> and Riser, Planques, and Barbier,<sup>3</sup> have speculated upon the interrelation between increased intracranial pressure, papilledema, and hypertension. It is generally agreed that increased intracranial pressure and papilledema usually occur together. However, their relation to the elevated blood pressure is not clear.

### METHOD AND MATERIAL

During the course of the clinical studies described in the previous papers of this series, twenty-five persons who had both hypertension and papilledema were observed. The cerebrospinal fluid pressure was measured directly in most of these cases, and was found to be elevated. On all of these subjects some of the studies described in Parts I through V, including capillary counts before and after giving histamine and measurements of cutaneous lymphatic flow, blood volume, and the amount of antidiuretic substance in the serum, were made. Not all of the procedures were carried out in every case because (1) some of the subjects were negroes, whose cutaneous pigmentation interfered with the capillary studies; (2) some of the patients were studied prior to the development of certain of the tests; and (3) it was considered inadvisable to measure the blood volume in some cases.

### RESULTS

1. Capillary mobility (as described in Part I). Capillary counts before and after the administration of histamine were made in sixteen cases. Capillary mobility was moderate in six, diminished in two, and high in eight.

2. Minute vessel pressure. This was measured in twenty-three cases, and found to be increased in twenty-one and normal in only two. The range was from 15 to 50 mm. of mercury, the average, 34. The effect of histamine was studied in seventeen instances. In five of these there was no significant change (less than 3 mm. of mercury), and, in the remainder, there were changes of 4 to 17 mm.

3. Cutaneous lymphatic flow was measured in fifteen cases. It was found to be increased in fourteen and normal in only one. One of the two subjects with normal minute vessel pressure and papilledema was found to have an increased cutaneous lymphatic flow; in the other the

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latter was not measured. The one patient with papilledema and a normal cutaneous lymphatic flow had an increased minute vessel pressure.

4. Blood volume was measured in fourteen cases. It was elevated in twelve and ranged from 80 to 108 c.c. per kilogram of body weight, with an average of 89 c.c. In two instances it was normal (62 and 72 c.c. per kilogram of body weight, respectively). In one of these cases there was no change in capillary count or pressure after histamine; this indicates a rather indistensible vascular bed. On the other patient, a negress, capillary studies could not be made.

5. The blood was examined for antidiuretic substance in fourteen cases. It was absent in seven cases and present in seven.

#### DISCUSSION

In the absence of a mass lesion of the brain, an increase in intracranial pressure may occur under the following conditions: (1) If there is so much increase in the formation of cerebrospinal fluid that absorption becomes inadequate, cerebrospinal fluid pressure will rise until an equilibrium is established, either by reducing further formation, or increasing absorption, or both. (2) If the absorption of cerebrospinal fluid into the blood stream or lymphatic system is decreased, cerebrospinal fluid pressure will rise until an equilibrium is established, either by reducing cerebrospinal fluid formation to a point below normal, or increasing absorption somewhat, or both. These possibilities will be considered separately.

In a previous series of articles,<sup>4, 5, 6, 7</sup> evidence concerning the mechanism of the production of papilledema was presented. This evidence suggested that papilledema could not occur in the absence of a patent space along the optic nerve, extending from, and in communication with, the cerebrospinal space. As the perineural, and probably perivascular, spaces function in the so-called "lymphatic" absorption of cerebrospinal fluid, the occurrence of papilledema means that the route of lymphatic absorption is not blocked.

There is no direct evidence to indicate that there is or is not interference with the absorption of cerebrospinal fluid into the blood stream in such cases.

There is direct evidence that there is an increased formation of cerebrospinal fluid. The evidence may be presented as follows:

1. In the experimental animal, when fluid enters the blood stream in such large amounts that it cannot be immediately excreted through the kidneys, or when elimination of smaller amounts of fluid is interfered with by some antidiuretic agent, hypertension has been shown to occur,<sup>8, 9</sup> and is associated with increased blood volume and increased intracranial pressure. The evidence seems to warrant the assumption that the increased intracranial pressure in such animals is caused by an increased formation of cerebrospinal fluid.



2. Clinically, papilledema occurs in association with hypertension in those cases in which there seems to be difficulty in eliminating fluid from the blood stream, either because an antidiuretic substance is present, or because of renal failure. In such cases there is a tendency toward increased minute vessel pressure, increased cutaneous lymphatic flow (showing increased loss of fluid from the capillaries), and elevated blood volume. These factors, if they were operating within the cerebrospinal space, would tend to produce edema of the brain and increased cerebrospinal fluid formation. Papilledema itself is probably nothing more than evidence of increased transfer of fluid from the cerebrospinal space along the perineural space of the optic nerve. To this may be added the effect of increased pressure on the central vein of the retina where it passes through this space.

If increased cerebrospinal fluid pressure is simply the intracranial concomitant of increased loss of fluid from the capillaries everywhere, one might expect it to occur in all persons with elevated minute vessel pressure and increased cutaneous lymphatic flow. Such is not the case. The explanation may be that (1) the tests, as outlined, are not capable of detecting quantitative differences sufficient to distinguish between patients who will, and patients who will not, develop papilledema; and (2) the cutaneous and intracranial circulation may share to a different extent in the general disease process. For example, if arteriolar spasm is more strongly maintained in the intracranial area than in the skin, the loss of fluid into the brain would be less than into the skin.

The disappearance of papilledema in two cases after pituitary irradiation may, of course, have been merely coincidence and spontaneous regression, but the more likely explanation is that excretion of fluid through the kidney was made easier as the antidiuretic substance disappeared, and hence the formation of cerebrospinal fluid was decreased.

#### SUMMARY

Increased intracranial pressure and papilledema occur in those cases of hypertension in which, as a rule, minute vessel pressure, cutaneous lymphatic flow, and blood volume are increased. In certain cases, such abnormalities are associated with the presence of an antidiuretic substance in the blood which is, perhaps, derived from the pituitary. In other cases there is renal disease. The evidence strongly supports the suggestion that the increased cerebrospinal fluid pressure is caused by increased cerebrospinal fluid formation. The evidence is definitely incompatible with the idea that papilledema is caused by diminished absorption of cerebrospinal fluid into the lymphatic system. The evidence neither favors nor opposes the possibility that there may be decreased absorption into the blood stream.

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## TREATMENT OF CONGESTIVE HEART FAILURE WITH AN ORALLY ADMINISTERED MERCURIAL DIURETIC

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ALTHOUGH the mercurial diuretics are unquestionably more effective when given parenterally than by any other route, the need for a potent diuretic which would require no special apparatus or procedure for its administration is evident. To the ambulatory patient who must have a diuretic frequently in order to remain free of edema, as well as to patients who are obese or have thrombosed veins, a mercurial diuretic which could be taken in some way other than by injection would be a boon. These considerations led to the development of mercurial suppositories as diuretic agents, and also prompted restudy of the oral administration of mercurial diuretics. Our remarks will be confined to the latter, for adequate observations on the suppositories are already available.

Calomel, advocated by Jendrassik,<sup>1</sup> in 1886, for the treatment of edema, was not only the first mercurial used for this purpose but also the first of its kind to be administered orally. The method of dosage, however (small amounts at frequent intervals), was somewhat hazardous, for it depended on the accumulation of sufficient mercury in the kidneys to initiate a diuretic action. Not only was the diuresis often unsatisfactory, but poisoning frequently occurred. Novasurol and salyrgan, when given orally, have little, if any, diuretic action.<sup>2</sup> As is the case with calomel, their mercurial fractions are altered by protein or the products of protein digestion within the gastrointestinal tract,<sup>2b, 2d</sup> so that the amount of absorption and, therefore, of diuresis is unpredictable. In addition, these compounds produce local irritating effects on the stomach and intestine which may result in ulceration or enterocolitis.<sup>3</sup>

In recent years the favorable influence of theophylline upon the diuretic effect and toxicity of mercurial diuretics which are administered parenterally has been established.<sup>4</sup> This fact prompted the observations of Chrometzka<sup>5</sup> and Görl<sup>6</sup> upon the oral use of such a combination. These authors reported favorably as to its effectiveness and safety. Their methods of study, i.e., using multiple doses for a period of a few days or weeks, do not permit, however, an adequate comparison with preparations which are given parenterally. Furthermore, evidence for their conclusion that the orally administered diuretic is milder and

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has a more prolonged action than those which are given intravenously is lacking. A study was therefore planned so that the diuretic effectiveness of oral, in contrast to parenteral, administration could be more accurately evaluated in the treatment of congestive heart failure.

#### METHOD

A single dose of five tablets of salyrgan-theophylline\* was given; each tablet contained 80 mg. of salyrgan (30 mg. of mercury) and 40 mg. of theophylline. The effectiveness and toxicity of this procedure were compared with the results of administering 1 or 2 c.c. of salyrgan-theophylline or mercupurin intravenously (mercury content approximately 40 mg. per c.c.). Forty-eight patients were studied; twenty-nine received the tablets; twenty-four, salyrgan-theophylline intravenously; and thirty, mercupurin intravenously. In twenty-two instances it was possible to compare the diuretic effect of the two methods of administration in the same patient.

The general plan of study for all mercurial diuretics has been previously reported in detail.<sup>4a, 7</sup> The salient features are, in brief, as follows. The diuretics were administered after a preliminary control period, during which the maximum effect of absolute rest in bed, oxygen, sedatives, limitation of fluid intake, dietary restrictions, ammonium chloride, and digitalis was ascertained. The dose of ammonium chloride, when it was used, was 1 to 2 Gm. three times a day. The urine was examined at frequent intervals for albumin and formed elements. When more than one diuretic was studied, the patient's weight was allowed to become constant or to return to the initial level before the second drug was given. The weight curve was found to be a more accurate index of the diuretic effect than the urinary output, because the latter tended to fluctuate widely. The weight was also a good guide to the amount of fluid available in the body for diuresis. A loss of 3 pounds, or more, in body weight within forty-eight hours of the administration of the diuretics was considered significant.

#### RESULTS

In a group of nine patients (Table I), the tablets were given whenever a diuretic was considered to be necessary, usually at intervals of three to five days. A satisfactory effect was obtained in all but one instance (third trial, No. 24), but even in this case further administration of the diuretic resulted in a good response. In two cases the tablets were administered four times, and, in one case, five times, without evidence of toxicity.

The effectiveness of the oral preparation was also compared with that of other diuretics (Table II). The results of using suppositories, which were obtained during a previous study,<sup>7</sup> are included. In approximately 72 per cent of the fifty-six trials with the salyrgan-theophylline tablets on twenty-nine patients a satisfactory diuresis was produced. The parenteral preparations were more consistently effective; they produced diuresis in approximately 90 to 95 per cent of the cases. It is also evident that the oral preparation of salyrgan-theophylline is more likely to cause satisfactory diuresis than the suppositories, which have an effectiveness of 50 to 63 per cent (Fig. 1).

\*Salyrgan-theophylline in enteric coated tablets (research number S. T. O. 3813) and in 1 c.c. ampules (research number S. T. 3833) was supplied by the Winthrop Chemical Company, Inc.

From a study of the number of trials (Fig. 2) which produced a definite diuresis, it is clear that oral administration causes a loss of 3 to 5 pounds in body weight; occasionally, the loss exceeds 8 pounds. The parenteral preparations, on the other hand, produce a greater diuresis, and weight losses of more than 8 pounds are common.

TABLE I  
DIURETIC EFFECTIVENESS OF SALYRGAN-THEOPHYLLINE, ADMINISTERED ORALLY

NO.	DIURETIC	DATE	NH <sub>4</sub> Cl	INITIAL WEIGHT (LB.)	WEIGHT FIRST DAY (LB.)	LOSS FIRST DAY (LB.)	MAX- IMUM LOSS (LB.)	DAYS
5	5 Tablets STO*	12/ 1/39	3	179	177	2	3	2
	5 Tablets STO	12/ 4/39	3	176½	172¾	3¾	7	3
	5 Tablets STO	12/14/39	3	163¼	159½	3¾	3¾	1
	5 Tablets STO	12/20/39	3	156½	154	2½	5½	2
11	5 Tablets STO	8/28/39	3	167	163½	4½	13	3
14	5 Tablets STO	9/13/39	3	215	212½	2½	10	3
20	5 Tablets STO	11/ 4/39	3	148½	144	4½	4½	1
	5 Tablets STO	11/ 7/39	3	143½	138	5½	5½	1
	5 Tablets STO	11/10/39	3	138	136¾	1½	5	3
22	5 Tablets STO	11/13/39	3	141½	139	2½	3½	2
23	5 Tablets STO	11/17/39	3	149¾	144	5¾	8¾	3
	5 Tablets STO	11/21/39	3	141	134	7	8½	3
24	5 Tablets STO	12/ 2/39	3	168½	161½	7	9¾	2
	5 Tablets STO	12/ 8/39	3	156½	150	6½	6½	1
	5 Tablets STO	12/12/39	3	150¼	148	2¼	2¼	1
	5 Tablets STO	12/15/39	3	148	144½	3½	3½	1
	5 Tablets STO	12/19/39	3	144½	138	6½	6½	1
25	5 Tablets STO	12/11/39	3	154¾	148½	6½	6½	1
	5 Tablets STO	12/15/39	3	148½	145½	3	3	1
26	5 Tablets STO	12/ 9/39	3	181½	174	7½	7½	1
	5 Tablets STO	12/13/39	3	174½	166½	8	11	3
	5 Tablets STO	12/18/39	3	163	156¼	6¾	6¾	1
	5 Tablets STO	12/21/39	3	159	150½	8½	8½	1

\*Enteric-coated salyrgan-theophylline preparation.

TABLE II  
COMPARATIVE EFFECTIVENESS OF MERCURIAL DIURETICS WHEN ADMINISTERED BY THE ORAL, PARENTERAL, AND RECTAL ROUTES

DIURETIC	NO. OF TRIALS	TRIALS SUCCESSFUL		NO. OF PATIENTS	PATIENTS SUCCESS- FULLY TREATED	
		NO.	PER CENT		NO.	PER CENT
Salyrgan-Theophylline by mouth (5 tablets)	56	40	71.5	29	22	75.8
Salyrgan-Theophylline intravenously	37	35	94.6	24	23	95.8
Mercupurin intravenously	60	55	91.7	30	29	96.6
Mercurin suppository	22	14	63.6	13	6	46.1
Salyrgan (modified) suppository	20	10	50.0	11	8	72.7

Although the onset and peak of diuresis after oral administration occurred slightly later than after parenteral injection, the diuresis was, in the majority of cases, complete within twenty-four hours. However, in 35 per cent of the trials a significant weight loss occurred within the second twenty-four hours.

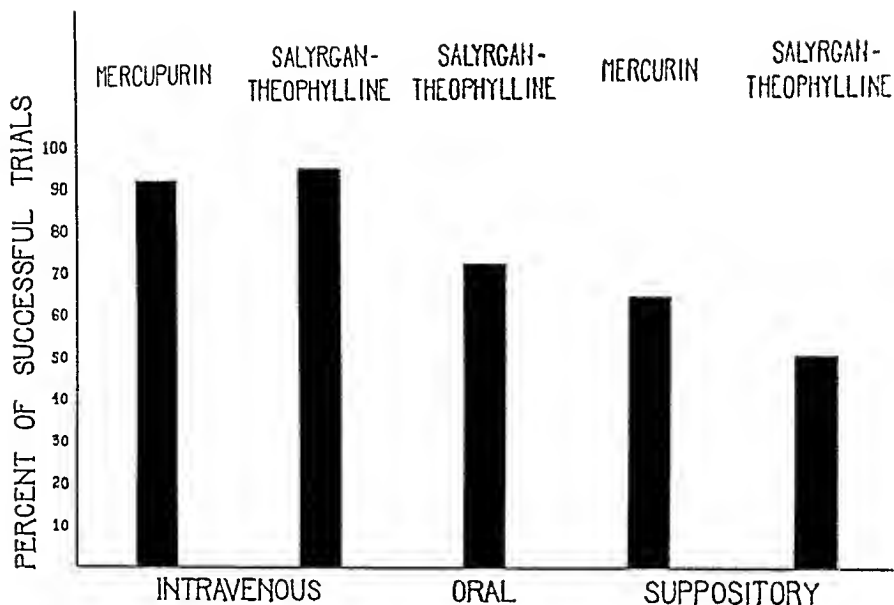


Fig. 1.—Comparative effectiveness of mercurial diuretics when administered by the intravenous, oral, and rectal routes.

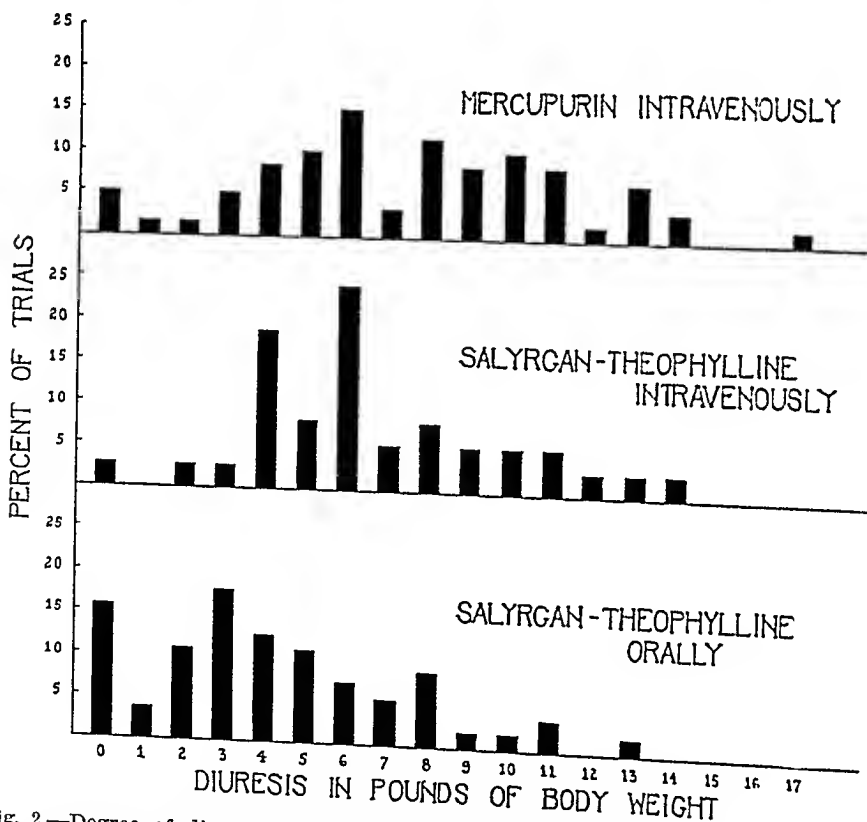


Fig. 2.—Degree of diuresis, as judged by weight lost, obtained by giving salyrgan-theophylline orally, and mercurpurin and salyrgan-theophylline intravenously.

The oral preparation failed to elicit a satisfactory response in sixteen instances, but in eight of these it was successful at other times. As was the case with the parenteral preparations, the previous administration of ammonium chloride and digitalis increased the effectiveness of the oral preparation. Although in several cases there was no apparent reason for failure, in others it appeared to be related to the advanced state of heart disease and lack of digitalis or of ammonium chloride.

Three patients experienced gastrointestinal symptoms after taking the tablets of salyrgan-theophylline. Two had diarrhea, and the other had epigastric discomfort, but in each case subsequent administration of the oral preparation was well borne. With the doses used, none of the patients showed any signs of renal irritation.

#### DISCUSSION

With the introduction of the oral preparation, four routes (intravenous, intramuscular, rectal, and oral) are now available for the administration of mercurial diuretics to patients with the edema of congestive heart failure. The modes of administration are not, of course, interchangeable to the extent that a satisfactory and comparable diuresis is obtained in every instance without regard to the preparation used or the state of the patient; one should select the method of administration which best suits the needs of each patient. The parenteral preparations are still the ones of choice whenever a rapid and marked diuresis is desired. They are, therefore, most suitable in cases of acute congestive heart failure, when immediate results are desired. For the patient with edema who is not acutely ill and does not require drastic measures for symptomatic relief, the oral preparation, because of its safety and efficacy, is suggested as the diuretic of choice. The unreliability of the mercurial suppository and the fact that it frequently causes rectal irritation<sup>7</sup> limit its usefulness. However, suppositories may occasionally be used to advantage when the patient cannot tolerate the oral preparation, or when there are contraindications or objections to parenteral administration.

The single dose of five tablets of salyrgan-theophylline (equivalent to 150 mg. of mercury) is by no means the dose recommended for all patients, but, when massive edema is present, it appears to be very satisfactory. For the ambulatory patient with a minimal amount of heart failure, this dose may be excessive. Therefore, further observations are now being made in order to ascertain the proper dose for prolonged treatment.

Gastrointestinal irritation occurs occasionally, and perhaps dividing the dose or giving a smaller one might result in diuresis without producing this untoward effect. Preliminary observations on animals have failed to reveal significant gastrointestinal irritation with doses several times as large as those used therapeutically. However, only studies on

ambulatory patients or patients with chronic congestive heart failure, over an extended period of time, will answer the question whether repeated use of the oral preparation is safe.

### CONCLUSIONS

1. Salyrgan-theophylline, when administered orally in doses equivalent to 150 mg. of mercury, is an effective and safe diuretic.
2. The diuresis is not only slower in its onset, but also more prolonged than after parenteral administration.
3. The diuretic effect is less than that produced by the parenteral preparations, but greater than with the suppositories.

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# ELECTROCARDIOGRAPHIC OBSERVATIONS ON ATHLETES BEFORE AND AFTER A SEASON OF PHYSICAL TRAINING

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THERE have been many electrocardiographic studies of the effects of exercise, but most of them have dealt with either the acute or remote chronic effects. In this investigation an attempt was made to detect any electrocardiographic changes which might be brought about by an entire season of physical training and athletic competition. The study was undertaken because of the frequent and persistent inquiries concerning the possibility that the heart may be injured by the rather long periods of sustained exertion which are required in the preparation for athletic competition.

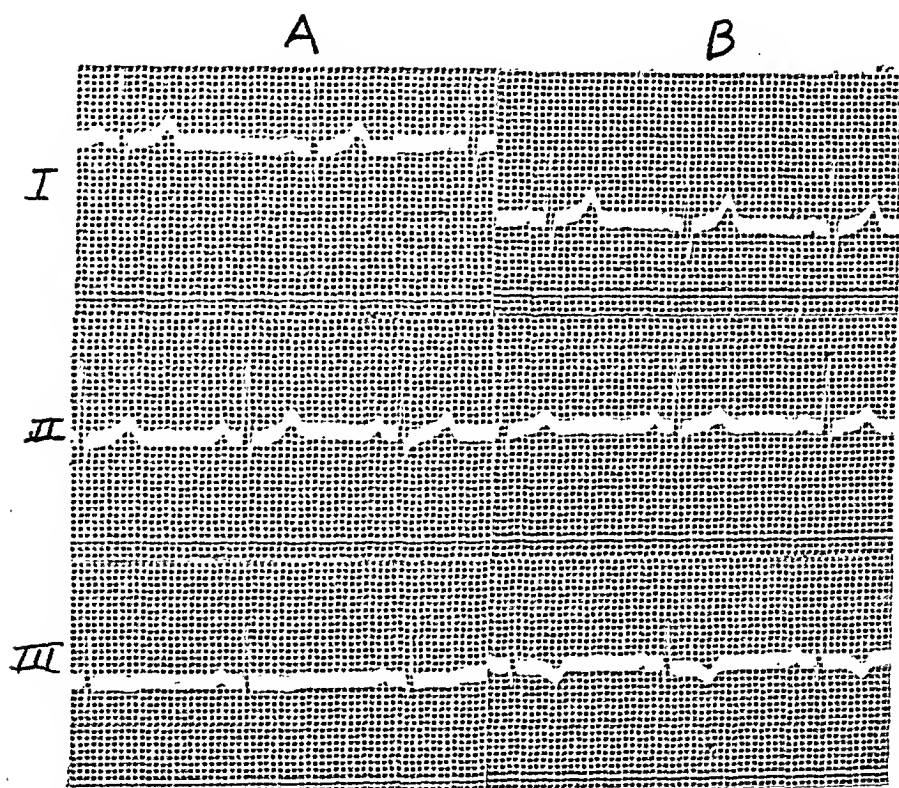


Fig. 1.—E. Me., aged 20 years, gymnast. A, before training. B, after training. Leads I and II did not change, but in Lead III the T wave became much more definitely inverted.

Kraus and Nicolai<sup>1</sup> found that the electrocardiograms of trained athletes, at rest, were practically the same as those of untrained subjects, except that the T wave tended to be higher. Messerle<sup>2</sup> reported that training not only caused the T wave to become higher, but lowered the

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ventricular peaks and greatly increased the duration of QRS. These variations were attributed to vagal influence. It is generally recognized, of course, that physical training decreases the resting heart rate. Hoogerwerf<sup>3</sup> summed up the situation concerning the effects of exercise on the heart by saying that, although many changes take place during exertion, they are not peculiar to the physically trained person but occur in the case of the untrained subject, also.

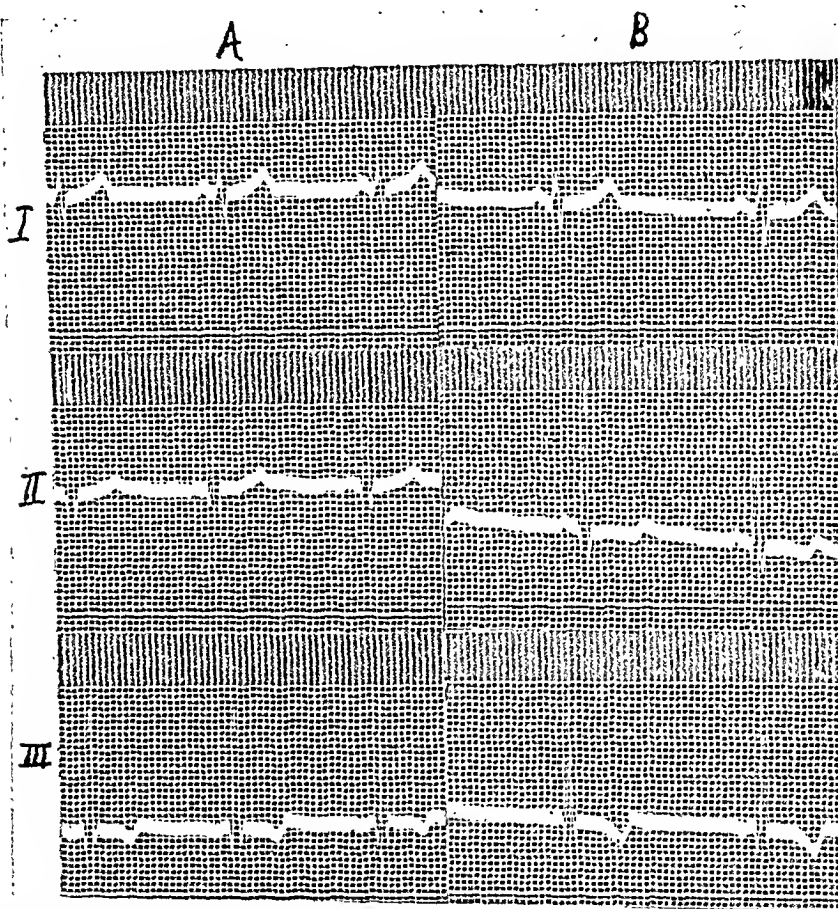


Fig. 2.—J. D., aged 21 years, basketball player. A, before training. B, after training. No change in Lead I. In Lead II the T wave became diphasic, and in Lead III the degree of inversion of the T wave increased.

Observations were made on forty-eight athletes, all of whom were healthy, normal, young men. There were four wrestlers, seven gymnasts, nine swimmers, six basketball players, and twenty-two track men. Each member of the group took part consistently in varsity competition. An electrocardiogram was made on each subject at the beginning of the training season, and again near the end, after strenuous training and active competition, when the men were in the pink of condition.

#### RESULTS

In forty-three cases there was no difference between the electrocardiograms which were made at the beginning of the training period and

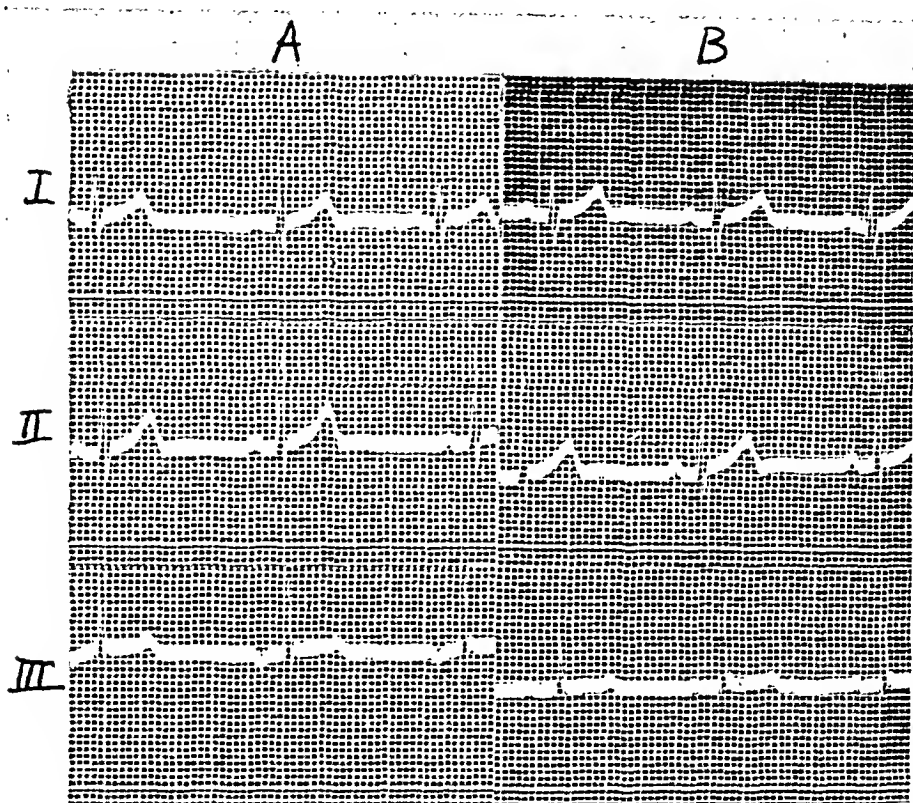


FIG. 3.—R. L., aged 20 years, swimmer. A, before training. B, after training. No change in Leads I and II. In Lead III, the P wave, which had been inverted, became upright.

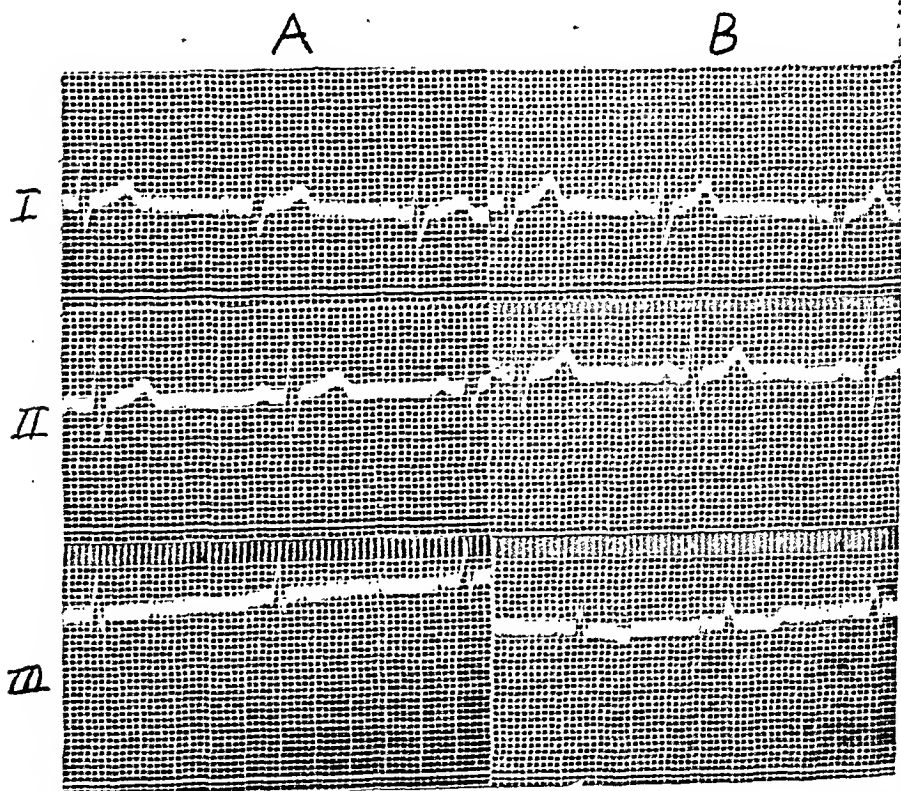


FIG. 4.—C. K., aged 21 years, wrestler. A, before training. B, after training. In Lead I the amplitude of the R and T waves increased slightly. No change in Lead II. In Lead III, the T wave, which had been isoelectric, became inverted.

those obtained when the men were at their peak. In one of the remaining cases the alterations were insignificant; the changes in the other four are depicted in Figs. 1, 2, 3, and 4.

#### CONCLUSIONS

Strenuous training and active competition produced slight electrocardiographic changes in four, or 8.3 per cent, of a group of forty-eight healthy young athletes. Although we have no explanation for these alterations, particularly those in the T wave, we have convinced ourselves that they were not indicative of myocardial injury. No two of these four men were engaged in the same sport.

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## ULCERATING VALVULAR LESIONS IN SUBACUTE BACTERIAL ENDOCARDITIS CAUSED BY THE STREPTOCOCCUS VIRIDANS

### REPORT OF A CASE

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ULCERATING valvular lesions in subacute bacterial endocarditis are not commonly encountered, and, aside from the writings of Libman, have received scant recognition in the literature.

Twenty-eight years ago, Libman<sup>1</sup> stated that in subacute bacterial endocarditis "ulceration of the aortic valve at times occurs; ulceration of the mitral valve is rare." In 1923, Libman<sup>2</sup> reiterated that "if ulceration does occur in subacute cases it is usually in the aortic flaps."

Boyd,<sup>3</sup> like Libman, has seen "a number of cases of ulcerating valvular lesions in subacute bacterial endocarditis." These, however, were confined to the aortic cusps. He has not observed any ulcerating lesions on the mitral valve in this disease. Gault<sup>4</sup> also recalls having seen two similar cases which he explains as follows: "It would appear that in certain persons the degree of tissue sensitivity to the toxin varies, and when extreme allergy is present, necrosis may be an important part of the lesion, with subsequent ulceration." Clawson<sup>5</sup> considered that the type of endocarditis is determined less by the kind of organism and more by its virulence.

In light of the above comments, the following case is reported.

### REPORT OF A CASE

W. W., a white man, aged 22 years, was admitted to the medical service of Dr. H. E. Waxman, at The Western Pennsylvania Hospital, Aug. 25, 1938, complaining of fever, chills, perspiration, and "a cold."

The patient gave a history of measles and chicken pox, as well as rheumatic fever at the age of four years. Because of frequent attacks of tonsillitis, the tonsils were removed in 1935. The family history was irrelevant. The patient smoked twenty cigarettes daily, and used alcohol moderately. He denied having had venereal disease. He was employed as a "chipper" in a steel mill and had worked eight hours daily until several days before admission. The work of a "chipper" consists of removing the rough surfaces of castings and is considered rather heavy manual labor. He had been told of his "heart condition" five years previously. Palpitation had been experienced at times, and, in the preceding two months, there had been occasional attacks of mild precordial pain. Three weeks before admission he had had an attack of "grippe," and had not felt well thereafter.

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He recalled seven definite occasions during that period when he had had attacks of fever, preceded or followed by chills, and with pronounced sweating. Four of these attacks occurred in the evening. He continued to work, but noticed progressive weakness and a weight loss of 20 pounds. Four days prior to admission he contracted an upper respiratory infection which added to his discomfort.

On admission the patient was found to be well-developed, muscular, well-nourished, and very pale. He lay comfortably in bed, although he appeared to be quite ill. He was perspiring profusely. Herpes were present about the mouth and nose. There were no conjunctival or cutaneous petechiae. Cardiac enlargement to the left was demonstrated by percussion. The heart sounds were of poor quality; at the apex there were an apical systolic and a diastolic murmur which were transmitted to the left axilla. The pulmonic second sound was accentuated. The blood pressure was 90/50. The abdomen was soft and full, and the spleen was palpable. A provisional diagnosis of bacterial endocarditis was made, and daily intravenous injections of sodium cacodylate (7.5 grains) were started and continued until the eighteenth day.

A septic temperature curve, ranging from 97° to 103.3° F., continued throughout the twenty-one days of hospitalization. The pulse rate varied from 64 to 112, and the respiratory rate, from 18 to 22. Immunotransfusions (typhoid) of 400 to 500 c.c. of blood were administered on the sixth, ninth, thirteenth, and seventeenth days. The last three transfusions were followed by chills. On admission the erythrocyte count was 4,410,000, and the hemoglobin, 85 per cent; on the ninth day, the erythrocyte count was 4,150,000, and the hemoglobin, 80 per cent; and on the twentieth day, the erythrocyte count was 3,060,000, and the hemoglobin, 60 per cent. The leucocyte counts on the same dates were 10,500, 7,700, and 21,100, respectively. A trace of albumin was found in the urine on two occasions, but there was no hematuria. A blood culture which was taken on admission showed 250 colonies of *Streptococcus viridans* per cubic centimeter; a second culture, six days later, showed 275 colonies per cubic centimeter; and a third, on the fifteenth hospital day, despite the intravenous medication, showed 285 colonies per cubic centimeter. The patient grew worse rapidly.

On the eighteenth day, the administration of acetyl sulfone (4,4'-diacetyldiaminodiphenylsulfone)\* orally, in doses of one gram three times a day, was begun. On the twenty-first day the patient died suddenly. A blood culture which was secured twelve hours ante mortem, after the administration of 7 grams of acetyl sulfone, exhibited twelve colonies of *Streptococcus viridans* per cubic centimeter, and another, taken nine hours post mortem, showed only three colonies per cubic centimeter. The appearance of growth in the last two cultures was delayed twenty-four hours, as compared to the first three cultures. The organism was carefully studied by Dr. Philip Hadley, who classified it as a *Streptococcus viridans*. No hemolytic zone was evident on aerobic or anaerobic media, and the bacterium was nonpathogenic for mice, rats, and guinea pigs. The virulence of the organism could not be enhanced by more than six successive mouse passages.

#### POST-MORTEM EXAMINATION

The body was that of a well-developed man; it weighed about 165 pounds and measured 175 cm. in length. The skin was moderately jaundiced. There were a few herpes about the nares, and some conjunctival petechiae. The heart weighed 575 grams and showed pronounced hypertrophy of the left ventricle and dilatation of all the chambers, particularly on the right side. The musculature of all of the chambers was moderately hypertrophied; the left ventricular wall averaged 2 cm. in thickness. The myocardium was reddish brown in color and soft in consistency. The aortic valve was bicuspid; its leaflets were markedly thickened, distorted, and adherent to each other. An aneurysmal pouching of the posterior cusp, with

\*Kindly supplied by the Monsanto Chemical Company, St. Louis, Missouri.

an irregular, ragged perforation measuring 0.5 cm. in diameter, was covered by a large, soft, friable, irregular, mottled, red and gray vegetation measuring about 2 cm. in diameter (Fig. 1). No inflammatory changes were present on any of the other valves. Focal, embolic glomerulonephritis, acute hepatitis and hepatomegaly (2825 grams), septic splenitis and splenomegaly (600 grams), with infarction, bilateral bronchopneumonia, bilateral hydrothorax, hydroperitoneum (300 c.c.), and hydropericardium (250 c.c.) were the other significant abnormalities.



Fig. 1.—Photograph of fixed heart, showing a deformed, bicuspid, aortic valve, with a probe extending through a perforation of the posterior cusp. A large, friable mass of vegetations covers the posterior cusp and part of the adjacent cusp.

*Microscopic Examination.*—The vegetations, in general, were of two types, namely, very recent ones, which showed the classical combination of fibrin, erythrocytes, leucocytes, and some monocytes, and definitely older ones, characterized, in some instances, by highly cellular and vascular granulation tissue (Fig. 2), and, in others, by cellular fibrous tissue (Fig. 3) in which inflammatory cells and vessels were much less abundant. The older vegetations were covered by endothelium. In some regions the older vegetations were the seat of a fibrinoid necrosis

of variable depth. This fibrinoid necrosis was also present in regions in which the endocardium was composed of acellular, hyalinized collagen. In addition to the vegetations, there were, on the ventricular and aortic aspects of the enspis, extensive subendocardial foci which showed extreme cellularity. Most of these cells were fibroblastic in type and were associated with many other mononucleated



Fig. 2.—Photomicrograph of vegetation, showing, in addition to marked cellularity, a high degree of vascularity indicative of early organization. (H & E  $\times 102$ .)

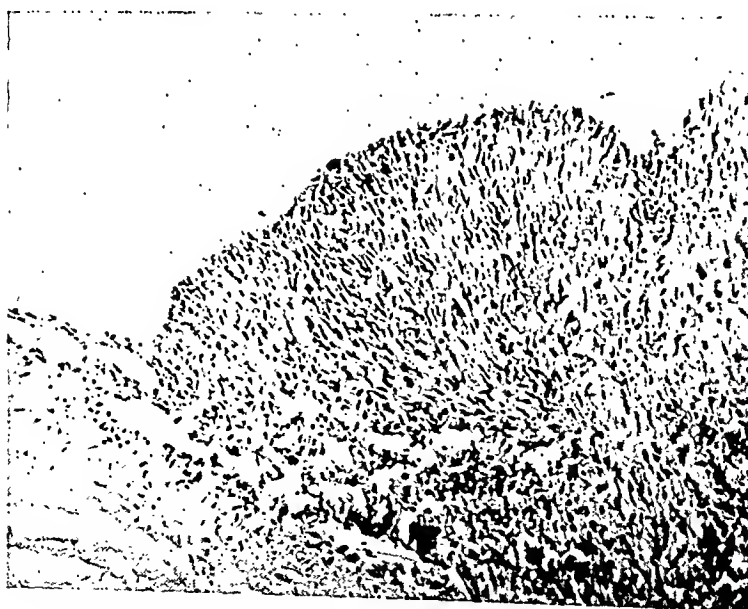


Fig. 3.—Photomicrograph of more advanced organization of a vegetation. (H & E  $\times 133$ .)

cells, but leucocytes were scanty. Occasionally, foci which varied in size from that of a half to several low-power fields contained leucocytes almost exclusively, and, in a few areas, leucocytes and monocytes were present in equal number; but, in general, mononucleated cells definitely outnumbered the others. In the region of the perforation there was a purulent necrosis which also involved the lower



portion of the sinus of Valsalva. A bacterial stain of the fresh vegetations showed cocci arranged singly and in chains of three and four. The bulk of the aortic valve consisted of acellular hyaline collagen and vascular fibrous tissue, with foci of calcification. Some sections of myocardium showed diffuse infiltration by acute inflammatory cells, frequent minute foci of necrosis, and occasional small accumulations of leucocytes. Subacute and chronic perivascular inflammation and perivascular fibrosis were often found. Petechiae, minute infarcts, and Aschoff bodies were not conspicuous. Several small vessels contained partially organized thrombi. The parietal endocardium showed moderate thickening and monocytic infiltration.

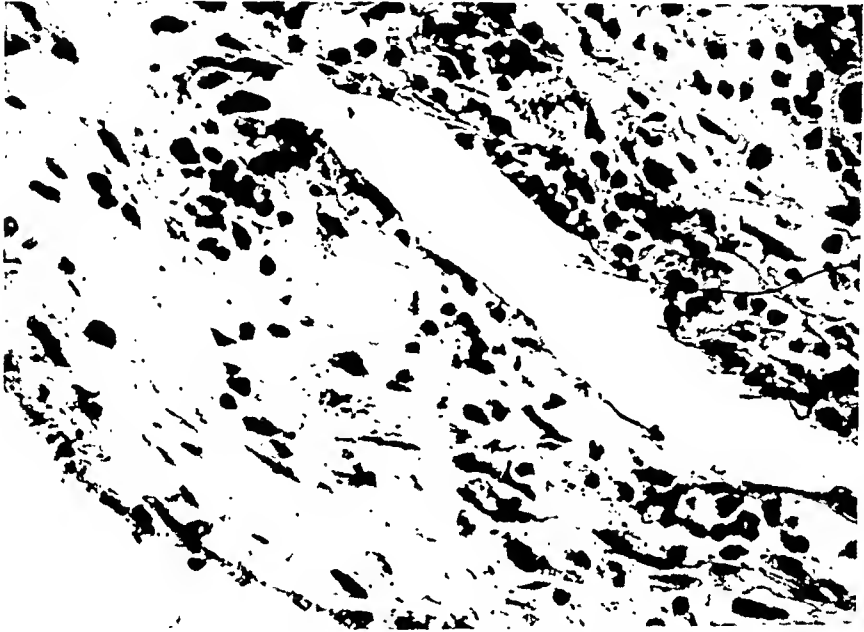


Fig. 4.—Higher magnification of granulation tissue seen in Fig. 2. (H & E  $\times 382$ .)

#### DISCUSSION

In attempting to classify this case as one of subacute bacterial endocarditis, several pertinent features are to be considered. Microscopically, various stages of organization were readily demonstrable in the vegetations. Of particular import was the presence of endocardial excrescences composed of capillaries with swollen endothelial cells, young, plump fibroblasts, and occasional monocytes and leucocytes in an edematous fibrillar stroma, which is so characteristic of young granulation tissue (Fig. 4). The five blood cultures, one of which was taken post mortem, showed pure growths of *Streptococcus viridans*. Furthermore, focal, embolic glomerulonephritis, which is associated exclusively with subacute bacterial endocarditis, was present in this case. The myocardial lesions were similar to those found by Saphir<sup>6</sup> in an analysis of thirty-five cases of subacute bacterial endocarditis. Pyemic phenomena, which are so commonly associated with acute ulcerative endocarditis, were absent.

Against the diagnosis of subacute bacterial endocarditis were the very bulkiness of the vegetations and a perforation of one of the cusps. It

is in reference to this perforation that the term "ulceration" has been used throughout this paper, and it should not be confused with the microscopic ulceration which is admittedly common in subacute bacterial endocarditis.<sup>5</sup> As was mentioned previously, Libman,<sup>1</sup> Boyd,<sup>3</sup> and Gault<sup>4</sup> have pointed out that the macroscopic type of ulceration occurs in subacute bacterial endocarditis.

Acute bacterial endocarditis may at times present features which are ordinarily characteristic of the subacute variety. Thus, Karsner<sup>7</sup> has seen evidence of organization in gonococci and pneumococci endocarditis when the duration of the disease was approximately three months. Ribbert,<sup>8</sup> in 1924, stated that from the anatomic point of view there are two types of endocarditis, namely, the verrucose and the ulcerative, although a sharp borderline between the two does not exist. He pointed out that, clinically, a sharp differentiation is also impossible, because, at times, in cases of subacute bacterial endocarditis, one is not able to ascertain during the life of the patient what form of the disease will be encountered at autopsy.

It is generally considered that the duration of subacute bacterial endocarditis is in excess of six weeks; yet the patient under discussion apparently died within that period of time. It must be remembered, however, that this subject was a robust, very muscular, hyposensitive person, and that therefore the duration of his illness was probably much longer than the history indicated.

Present-day treatment of this disease is just as varied as it is ineffective. Capps<sup>9</sup> tabulated sixty-seven reported cures which lasted one year or more, and added seven more patients from his own series who survived more than five years. Of the total of seventy-four cases, there was no specific therapy in twenty-nine, in eighteen the mode of treatment was not stated, and in the remaining twenty-seven cases various agents were used, including sodium cacodylate, vaccines, normal sera, salvarsan, radium, and immunotransfusions.

In evaluating any instance of recovery from subacute bacterial endocarditis, the deductions of Clawson and Bell<sup>10</sup> must be taken into consideration. From a series of thirty-five cases of acute rheumatic fever and eighty cases of subacute bacterial endocarditis, they concluded that the coexistence of bacteremia and endocarditis does not necessarily mean that the patient has what is clinically recognized as subacute bacterial endocarditis; and that the streptococcus, generally the viridans strain, seems to be responsible for both the rheumatic and subacute bacterial forms.

The drug (acetyl sulfone) which was administered in this case has been used to some extent in France for the treatment of gonorrhea. Its action has been investigated by Cooper, Gross, and Lewis,<sup>11</sup> who found that it was more effective than sulfanilamide in the treatment of hemolytic streptococcal infections in animals. In this case, coincident with

the medication, there was a marked diminution in the number of colonies of *Streptococcus viridans*, but bacteria were readily found in the vegetations. The employment of this drug in several other cases in this institution resulted only in a temporary decrease of the blood bacterial count.

In conclusion, the experiments of MacNeal and his associates,<sup>12</sup> in which vegetative endocarditis was produced in rabbits by repeated intravenous injections of serum-broth cultures of *Streptococcus viridans*, should be mentioned. Among the resultant lesions were various stages of growth and healing of vegetations. MacNeal<sup>13, 14</sup> feels that these lesions were identical with those of human subacute bacterial endocarditis. He<sup>15</sup> suggests that classification of diseases of the heart valves should be etiologic, and that, therefore, one should speak of a vegetative endocarditis caused by the *Streptococcus viridans*.

#### CONCLUSIONS

1. Perforation of the aortic valve in a case of subacute bacterial endocarditis caused by the *Streptococcus viridans* is reported.

2. The difficulty of classifying anatomic lesions under the heading of subacute bacterial endocarditis, in the light of expert opinion and recent experimental work, is discussed.

3. In this case, the administration of 4,4'-diacetyldiaminodiphenyl-sulfone was accompanied by a marked drop in blood bacterial content.

The author wishes to express his gratitude to Dr. H. E. Waxman for permission to report this case.

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# SYSTOLIC GALLOP RHYTHM AS A SIGN OF ANEURYSM OF THE LEFT VENTRICLE

## REPORT OF A CASE\*

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**S**YSTOLIC gallop rhythms, when the extra sound is loudest at the apex, are generally thought to be of no clinical significance. It is our purpose in this report to present the record of patient with such a rhythm, caused, apparently, by an aneurysm of the left ventricle. It should be mentioned that, when the gallop was perceived, we did not think that it was of any consequence. The investigation was carried out in the hope of being able to ascertain, with the use of modern instruments, the origin of the ectopic sound.

## REPORT OF CASE

The patient, a 52-year-old colored man, was first seen May 14, 1938. He had been referred to us for an opinion as to whether arsenicals should be administered as a part of the treatment of his latent syphilis. At that time he had no symptoms of heart disease. His health had always been good, but he had acquired a urethral chancre in 1918. He was unable to recall having had any secondary manifestations of syphilis. In 1934, it was discovered that his blood Wassermann reaction was positive, and he received antisyphilitic treatment for two months. Early neurosyphilis then was diagnosed, and he was sent to a state hospital, where he remained for six months. During this time he was given sixteen "fever" treatments and sixteen injections each of a bismuth compound, a mercury compound, and nearsphenamine. After he was discharged from this institution, he was in good health, and resumed his usual occupation as a porter in a railroad station. In February, 1938, the blood Wassermann and Kahn reactions were found to be positive, and he was advised to resume treatment.

On physical examination the patient was found to be a tall, spare, well-muscled, and apparently healthy, colored man. There were no skin lesions. His pupils were circular, equal, and reacted to light and in accommodation. There were no mucous patches or other lesions in the oral cavity. His teeth were in good condition. Examination of the anus, rectum, and external genitalia showed nothing abnormal. All of the deep tendon reflexes were present, and there was no Romberg sign. The lungs and the abdomen were normal. The accessible arteries were moderately thickened and somewhat tortuous. The apex impulse of the heart was seen and felt in the fifth intercostal space about 9 to 10 cm. to the left of the midsternal line. Percussion showed no enlargement of the heart or aorta. The blood pressure, in the sitting position, was 120/64 in both arms. The pulse rate at rest varied from 56 to 64 per minute. The heart tones at the base were distant, distinct, and apparently normal. The sounds at the apex attracted attention. There one heard a sharp tone almost midway between the first and the second heart sounds. Its intensity approximated that of the second sound. It could be heard from the apex

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to the lower part of the left border of the sternum but was diminished in intensity in the latter region. Change in posture, exercise, and the Valsalva experiment had no influence on the quality or duration of the extra heart sound. Examination of the urine on several occasions revealed no abnormality. A teleroentgenogram which was made in June, 1938, revealed no enlargement of the heart but disclosed a prominent aortic "knuckle." Roentgenologically, the lungs and great vessels were normal. The shadow of the left ventricle, at that time, aroused no suspicion. Electrocardiograms were made on several occasions and were interpreted as showing normal mechanism, with infrequent extrasystoles of supraventricular origin.

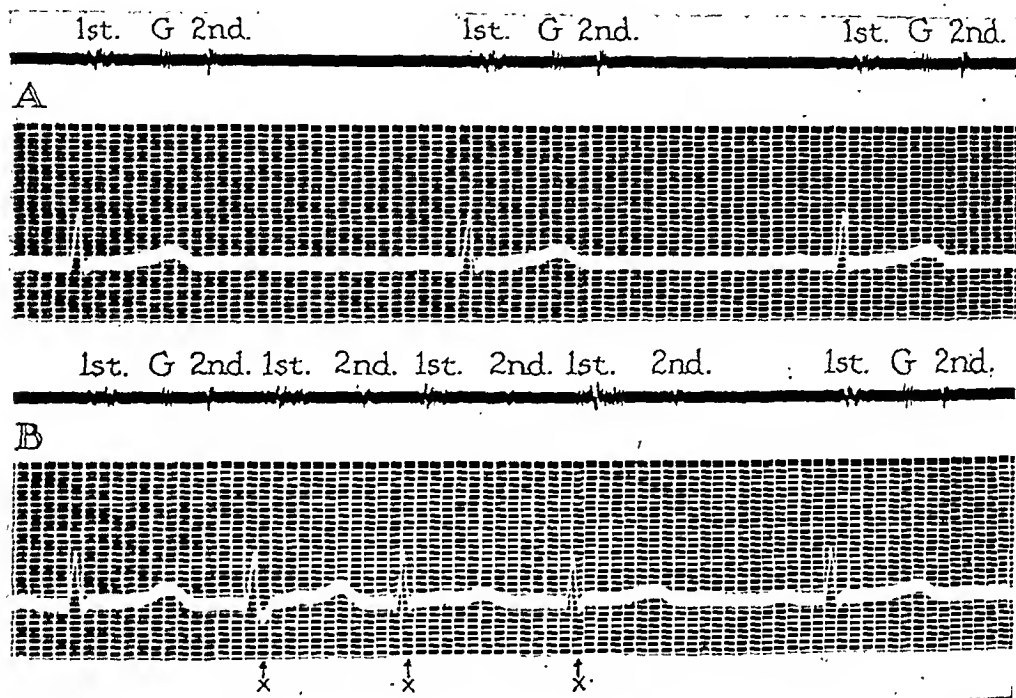


Fig. 1.—Simultaneous stethogram and electrocardiogram showing: A, Systolic gallop sound (G). B, Three successive supraventricular extrasystoles (X) which produced no gallop sound.

Further studies to ascertain the cause of the systolic gallop rhythm were then undertaken. Fluoroscopic examination of the heart disclosed a small (4 to 5 cm. long) aneurysm of the lateral wall of the left ventricle, with characteristic outpouching during ventricular systole. The other motions of the heart were normal. The aorta was seen to be elongated and moderately dilated, but the radioscopist, Dr. E. E. Barth, thought that aortic atherosclerosis, and not syphilitic aortitis, was responsible for this alteration. Simultaneous stethographic and electrocardiographic records fully confirmed our clinical impression that the gallop sound occurred between the first and second heart sounds. While one of the records was being taken, several consecutive extrasystoles of supraventricular origin occurred. During this time there was no gallop. Efforts to produce extrasystoles were unsuccessful. Electrocardiograms, jugular phlebograms, femoral arteriograms, digital (great toe) plethysmograms, and apex cardiograms were made simultaneously. Fortunately, on one occasion, when we were recording the arterial pulse, digital pulse volume, and electrocardiogram, an isolated extrasystole occurred. Finally, a roentgenkymogram was made while an electrocardiogram was being recorded. The results of these studies can be summarized briefly, as follows:

1. The stethographic record of the gallop sound consisted of four or five spikes which lasted 0.04 sec. The dominant frequency was 100 to 125 double vibrations

per second. In intensity and general appearance it was similar to the second heart sound. The gallop occurred 0.24 sec. after the onset of the QRS complex, 0.18 sec. after the commencement of the first sound, and 0.16 sec. before the beginning of the second sound. Thus, it was a true systolic gallop rhythm (Fig. 1).

2. Comparison of the jugular phlebogram, the electrocardiogram, and the stethogram revealed no right auricular activity that might account for the gallop (Fig. 2A).

3. Comparison of the stethogram with the apex cardiogram disclosed no motion of the chest wall which was simultaneous with the gallop. Thus, the extra heart sound was not caused by impact of the heart against the thoracic wall (Fig. 2B).

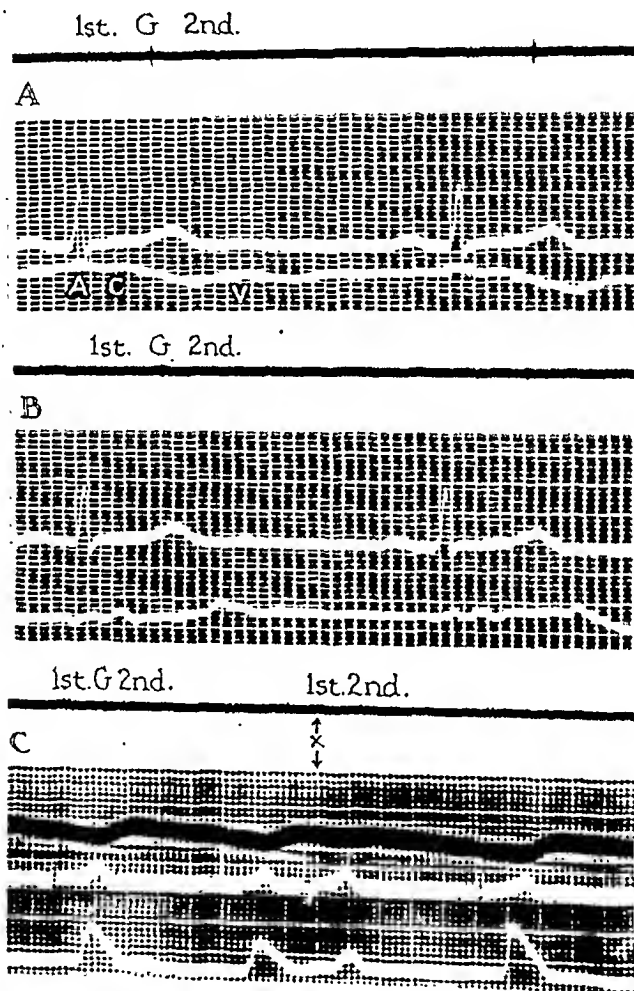


Fig. 2.—A, Simultaneous stethogram, electrocardiogram, and right jugular phlebogram. B, Simultaneous stethogram, electrocardiogram, and apex cardiogram. C, Simultaneous stethogram, digital plethysmogram, electrocardiogram, and femoral arteriogram, showing a hypodynamic supraventricular extrasystole (X).

4. Examination of the roentgenkymogram revealed typical paradoxical movement of the wall of the left ventricle, commencing 0.14 sec. after the onset of ventricular systole, when the heart rate was 60 per minute. The maximum outward motion of the aneurysm occurred 0.28 sec. after the onset of systole. The gallop occurred during this interval (Fig. 3).

5. The gallop also coincided with aortic filling, but the extra sound was heard very faintly over the aorta and could not possibly have been caused by the impact of the aorta against neighboring structures.

It was fairly apparent, therefore, that the gallop was in some way related to the outward motion of the aneurysm of the left ventricle. We made several assumptions in an attempt to explain the production of the gallop sound, as follows:

1. The aneurysm was approximately at the site of the attachment of the anterior papillary muscle (upper part).

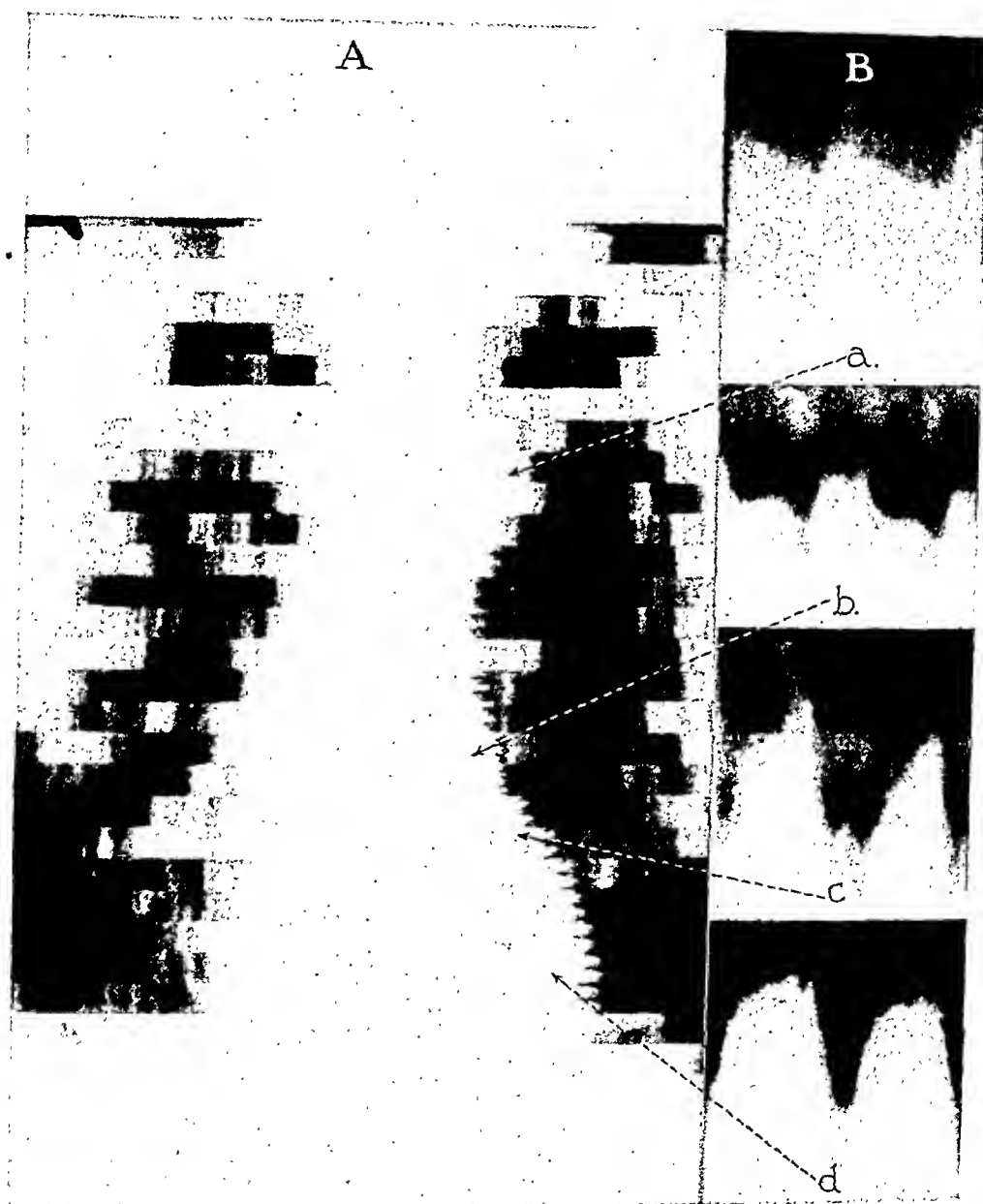


Fig. 3.—A, Roentgenkymogram, showing paradoxical movement of left ventricle (area c). B, Enlargements of areas from the border of the kymogram arranged to show simultaneous movements: a, aortic arch; b, left auricular appendage (or left auricle); c, left ventricular aneurysm; d, apex of left ventricle. Upward movement on the kymographic enlargements represents cardiac filling. Time relations from left to right.

2. The gallop occurred at a time in the cardiac cycle when the ventricle was almost empty, when intraventricular pressure was still very high, and when the papillary muscles were under great tension.

3. Towards the end of systole, when the aneurysm suddenly bulged outward, it carried with it the attachment of the anterior papillary muscle. This should have deformed the anterior leaflet of the mitral valve, permitting a sudden reflux of blood into the left auricle. The latter is quite possible, for left intraauricular pressure is much less than aortic pressure.

This idea, namely, that a deformity of the mitral valve, with a sudden reflux of blood into the left auricle, may cause gallop, gains support from two widely different observations, to wit:

1. As was noted previously, the gallop failed to occur when an extrasystole occurred (Fig. 1B); extrasystoles are hypodynamic. The simultaneously recorded femoral arteriogram, digital (great toe) plethysmogram, and electrocardiogram showed one premature beat of supraventricular origin, and it may be seen readily that the amplitude of the femoral and digital pulses was considerably less than usual (Fig. 2C). This observation suggests that, when the premature ventricular contraction occurred, the pressure in the left ventricle was less than usual, and we find no difficulty in assuming, further, that the ventricular pressure was not high enough to produce the distortion of the anterior mitral leaflet which is necessary for the production of the gallop.

2. Inspection of the roentgenkymographic silhouette of the left auricle (or of the left auricular appendage) disclosed a sudden, short, outward motion which was coincident with the maximum outward thrust of the aneurysm (Fig. 3). This extra peak is not seen in normal roentgenkymograms, and is, we believe, a result of the reflux of blood from the left ventricle into the left auricle.

In our opinion, the combination of direct and circumstantial evidence that has been presented is sufficient to explain the genesis of the gallop rhythm in this case. Systolic gallop rhythm is generally held to be purely incidental, but we believe that it may be a sign of aneurysm of the left ventricle.

#### CONCLUSIONS

1. In this case, a careful search for the cause of systolic gallop rhythm led to the discovery of an aneurysm of the left ventricle and suggested that such an aneurysm, by distorting the mitral valve during systole, may cause gallop rhythm.

2. In this case, at least, the systolic gallop rhythm at the apex was certainly a sign of a pathologic process, namely, aneurysm of the left ventricle.



# Department of Reviews and Abstracts

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## Selected Abstracts

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Wégria, René, and Wiggers, Carl J.: Factors Determining the Production of Ventricular Fibrillation by Direct Currents. (With a Note on Chronaxie.) *Am. J. Physiol.* 131: 104, 1940.

This research was designed to establish, as far as possible, the conditions under which ventricular fibrillation is produced by direct currents of different durations and to offer a logical explanation for its occurrence. For this purpose D. C. shocks ranging from 1 to 50 Ma. were applied for intervals of 0.01 to 0.33 second to a small area of dogs' left ventricles by nonpolarizable electrodes. Shocks were introduced in alternating directions at every sixth ventricular beat and were so spaced that they fell progressively earlier or later in relation to normal cycles. In this way, the incidence of closing and opening as well as duration of action could be established. Our analysis leads to the following conclusions:

1. The dominant factor which determines the induction of ventricular fibrillation by an electrical stimulus is the fact that any type of stimulus above a certain critical value, introduced during the vulnerable period of late systole, causes simultaneously a premature contraction plus some local or generalized disturbance of conduction which permits irregular re-entry of impulses and leads to the various stages of fibrillation described by one of us.

In the case of direct currents, the effective excitant may be (a) a brief rectilinear shock, probably not more than 0.04 second in duration or (b) the closing or opening of more prolonged currents during this period of vulnerability.

In the case of D. C. stimuli which exceed 0.05 or 0.06 second, several secondary factors may enter which also lead to fibrillation.

The factor which determines fibrillation in any specific instance depends upon the duration of the D. C. stimulus, upon the time that closure occurs with respect to the cycle, upon the character of the premature response evoked, upon the relation of opening to a normal or premature beat, etc. However, we believe that it can be demonstrated in many of these highly variable conditions, and is probable in others which cannot be so definitely analyzed, that a second effective stimulus, artificial or physiologic, must strike during the vulnerable period of a premature systole in order to cause fibrillation. Such a concept harmonizes the apparent discrepancy that brief shocks of any form only cause fibrillation when they are applied during the vulnerable period, whereas D. C. shocks longer than 0.05 second may do so, when they fall entirely in diastole, partly in systole and partly in diastole, or even when they extend over several beats.

The chief secondary mechanisms by which shocks longer than 0.05 or 0.06 second become more potent fibrillation stimuli, are fundamentally due to two well-known peculiarities of such shocks: 1. They are no longer unitary stimuli but are capable of exerting separate C and O effects, and 2, they cause effects (electrotonic?) during persistence of the current, which give rise to unpredictable spontaneous impulses either during the flow of the current or shortly after its cessation.

The manner in which such secondary phenomena lead to fibrillation with currents of increasing duration (0.07-0.33 sec.) is graphically depicted in Fig. 2. In a broad way, these conditions can be summarized verbally as follows:

(A) When C, falling during the vulnerable phase or early diastole, causes a premature contraction of such duration that O of effective strength occurs during its vulnerable period.

(B) When C occurs during the refractory period of a normal cycle, but the continued passage of the current causes a spontaneous premature beat in the next or any subsequent diastole and O occurs during its vulnerable period.

(C) When C occurs during the refractory period of a normal cycle and O falls during early diastole of this or any subsequent beat causing a premature contraction and later a spontaneous premature impulse which coincides with the vulnerable period of the first premature beat due to O.

In view of (a) the greater tendency even of weak currents, 0.24-0.33 second in duration, to evoke spontaneous premature beats not related to C or O; (b) the frequency of fibrillation by such currents in our series and (c) the nonexistence in the beating heart of any span of iso-excitability, the determination of chronaxie of the ventricles by use of direct currents introduces difficulties.

AUTHORS.

Wégria, René, and Wiggers, Carl J.: Production of Ventricular Fibrillation by Alternating Currents. *Am. J. Physiol.* 131: 119, 1940.

The effects of 60 cycle alternating currents applied locally to the dog's left ventricle through nonpolarizable electrodes are analyzed:

A. C. stimuli composed of  $\frac{1}{2}$  to 4 waves (0.008-0.0666 sec.), like brief D. C. shocks, act as a unitary stimulus. When they start or fall entirely within the vulnerable period, they always give a response if strong enough; that response is one or two premature ventricular systoles followed or not by ventricular fibrillation. The influence of the moment of onset or phase angle in relation to the vulnerable period has not been established. A similar stimulus during the refractory period is ineffective. When given during diastole, it causes one premature beat and never produces fibrillation.

Stimuli composed of more sine waves (generally 7 to 9) produce no effect or an occasional premature beat when they are very weak. A similar number, of moderate strength, falling entirely in the refractory phase are ineffective; but when they encroach upon, cover, or start in the vulnerable period, they evoke a single premature contraction, but never cause fibrillation. If they start ever so early in diastole, however, fibrillation occurs. Strong currents also cause fibrillation when they enter during the vulnerable period.

The occurrence of fibrillation by early diastolic shocks, incapable of acting during the vulnerable period, can be explained by the fact that an effective portion of the series now falls during the vulnerable of a premature beat. In other words, an apparent diastolic fibrillation is actually a fibrillation started during the systolic vulnerable period of a premature beat.

A. C. stimuli, with durations varying from 0.2 to 1 second or more, promptly cause fibrillation when currents are of moderate or great strength. However, even very weak currents (0.5 to 1.0 Ma.) cause ventricular tachycardia which may revert to a normal rhythm after removal of the stimulus or may eventuate in fibrillation either while the A. C. is operating or shortly after its withdrawal.

An analysis of the ventricular tachycardia reveals that the rhythm is not quite regular and that a tendency to progressive increase in rate occurs. In some instances, electrical alternation exists and a peculiar dissociation of electrical and left

ventricular pressure occurs in alternate beats, despite the fact that electrodes are applied to the left ventricle. Therefore, the probability is weighed that the tachycardia is caused by re-entry rather than by periodic focal stimuli. However, conclusive evidence for such a theory is not adduced.

The reason why weak alternating currents produce fibrillation in some tests and not in others remains obscure. However, definite evidence is presented that the duration of such currents is not a factor provided this exceeds 0.2 sec. The mechanisms through which fibrillation eventuates during or shortly after use of such weak A. C. currents are difficult to analyze on the basis of evidence so far available.

AUTHORS.

**Schroeder, Henry A., and Steele, J. Murray:** The Behavior of Renal Blood Flow After Partial Constriction of the Renal Artery. *J. Exper. Med.* 72: 707, 1940.

Studies have been made of the behavior of renal blood flow after partial constriction of the renal artery in twenty-four dogs.

When reduction in renal blood flow is produced by partial constriction of the renal artery, a readjustment of flow in the direction of normal occurs within a few minutes, subsequent constriction being again followed by a return of flow toward normal until the artery is markedly constricted.

Renal blood flow after marked constriction of the artery becomes extremely susceptible to the vasoconstrictive action of small doses of adrenalin, and flow may cease with larger doses for a considerable period of time.

Arterial hypertension of significant degree may follow partial constriction of one renal artery during brief experiments when adrenalin in addition has been administered.

Further evidence is presented in favor of the concept that the renal circulation enjoys a control independent of systemic arterial pressure.

AUTHORS.

**Squire, J. R.:** An Instrument for Measuring the Quantity of Blood and Its Degree of Oxygenation in the Web of the Hand. *Clin. Sc.* 4: 331, 1940.

An instrument is described by which the light transmission through the web of the hand is measured at two different spectral regions. From this, the quantity of blood present and its degree of oxygenation are calculated. The apparatus is portable and suitable for clinical investigations.

AUTHOR.

**Steincrohn, Peter J.:** A New Observation Helpful in the Diagnosis of Coronary Thrombosis. *Ann. Int. Med.* 14: 495, 1940.

Descriptions of coronary thrombosis pain in the literature do not mention or stress the importance of evaluating the quality of this pain.

The outstanding characteristic of this pain is its rhythm and periodicity.

The patient must be observed carefully before the presence of these characteristics can be determined.

If the periodicity of these pains is observed, the diagnosis can be made and will be substantiated later by positive evidence.

An analysis of six patients has been made to describe this pain syndrome.

AUTHOR.

**Hedley, O. F.:** Rheumatic Heart Disease in Philadelphia Hospitals. *Public Health Reports* 55: 1599, 1940.

During the five-year period from January 1, 1930, to December 31, 1934, there were 5,921 admissions involving rheumatic heart disease, rheumatic fever, Syden-

ham's chorea, and subacute bacterial endocarditis to thirty-six hospitals in Philadelphia. Of these admissions, 5,801 were for rheumatic heart disease, rheumatic fever, Sydenham's chorea, and subacute bacterial endocarditis on a rheumatic basis, while 120 were for subacute bacterial endocarditis in which a definite relationship to rheumatic heart disease was not determined.

Comment is made on difficulties in terminology in describing rheumatic conditions, and on the variety of combinations in which they occur. Considerable improvement in diagnostic standards and in the maintenance of hospital records was noted during the period under study.

The diseases under study were indicated in 0.70 per cent of admissions from all causes to Philadelphia hospitals. In three children's hospitals they were present in 1.56 per cent of all admissions. In fourteen teaching hospitals these conditions were noted in 0.79 per cent of all admissions. Most of the admissions were to the large general and children's hospitals located in the center of the city.

It is estimated that the conditions under study were present in 2.4 per cent of medical admissions to general hospitals and 5.8 per cent of medical admissions to children's hospitals.

Rheumatic heart disease, rheumatic fever, and Sydenham's chorea were the principal causes of 87.2 per cent of these admissions, while subacute bacterial endocarditis was the principal cause of 5.8 per cent of the 5,921 admissions constituting this series. Practically all admissions involving rheumatic fever and chorea were caused primarily by those conditions.

Over 93 per cent of admissions involving rheumatic conditions were to the wards of general and children's hospitals. This substantiates the view that rheumatic heart disease is essentially a problem of the class of patients treated on hospital wards.

The total number of admissions to Philadelphia hospitals for rheumatic heart disease, rheumatic fever, Sydenham's chorea, and subacute bacterial endocarditis, most of which is superimposed on rheumatic heart disease, is probably slightly over 1,200 a year; of these, over 900 are first admission.

It is estimated that rheumatic conditions and subacute bacterial endocarditis were factors in 272,000 patient-days in Philadelphia hospitals during this five-year period. Of this number, only about 5,000 patient-days were due to subacute bacterial endocarditis not superimposed on rheumatic heart disease. It is estimated that rheumatic conditions were in varying degrees accountable for 187,000 patient-days in general hospitals and 23,700 patient-days in children's hospitals. They result in over 40,000 patient-days annually in general and children's hospitals. In addition, there were about 61,300 patient-days caused by rheumatic conditions at the Children's Heart Hospital, a sanitarium furnishing prolonged convalescent care. Including this institution, rheumatic conditions account for, or at least are concerned in, over 50,000 patient-days each year in Philadelphia hospitals.

It is estimated that the conditions under study accounted for or were responsible factors in 2.0 per cent of patient-days in general and 7.5 per cent in children's hospitals.

The estimated cost of hospitalization of patients with these conditions is over \$272,000 a year, exclusive of physicians' services, most of which are rendered gratuitously.

Prolonged convalescent care is furnished such a small percentage of patients with rheumatic fever, chorea, and rheumatic heart disease that it is not possible to evaluate its benefit. Of the fatal cases under 20 years of age, only 13.6 per cent had been admitted to that institution.

Hedley, O. F.: Rheumatic Heart Disease in Philadelphia Hospitals. II. Age, Race, and Sex Distribution and Interrelation of Rheumatic Fever, Sydenham's Chorea, Rheumatic Heart Disease, and Subacute Bacterial Endocarditis. Public Health Reports 55: 1647, 1940.

An analysis has been made of the age, race, and sex distribution of rheumatic fever, Sydenham's chorea and rheumatic heart disease in Philadelphia hospitals from January 1, 1930, to December 31, 1934, based on the age at initial admission during the period under study and the age at onset as indicated in the clinical histories. In some cases the onset occurred during stay in hospital; in other instances it was determined by review of patients' past histories. Figures have been prepared showing the age distribution and cumulative percentages by five-year age periods of a number of important rheumatic manifestations.

The literature has been reviewed and tables prepared showing the association of rheumatic fever and clinical manifestations of rheumatic heart disease, the age at onset of rheumatic infections, the percentage of Sydenham's chorea presenting clinical evidence of rheumatic heart disease, the percentage of rheumatic heart disease with histories of rheumatic fever and Sydenham's chorea, and the percentage of subacute bacterial endocarditis superimposed on rheumatic heart disease.

The importance of rheumatic heart disease as a problem of childhood and youth is emphasized by the fact that the onset of 76.4 per cent of rheumatic fever, 98.2 per cent of chorea, and 69.1 per cent of rheumatic heart disease occurred before age 20. The mode of the age of onset of rheumatic fever was 8.7 years, of Sydenham's chorea 9.3 years, and of rheumatic heart disease 8.9 years. Of the initial admissions during the period under study (not necessarily the first admissions for these conditions), 59.6 per cent of rheumatic heart disease occurred among persons under 20 years of age. Despite the fact that this is the first study on a large scale of the major rheumatic manifestations at all ages, the peak of onset of rheumatic fever, Sydenham's chorea and rheumatic heart disease occurred in the 5 to 9 year age period.

The expression "juvenile rheumatism" is regarded as an inappropriate description of a disease which begins for the most part during childhood, but is characterized by chronicity, exacerbations, and recurrences throughout adult life. Although essentially a problem of childhood, and youth, attacks of rheumatic fever may occur at almost any age.

In only 2.7 per cent of cases of rheumatic fever and 5.7 per cent of cases of rheumatic heart disease did the onset occur after age 40. Rheumatic heart disease is decidedly infrequent among hospital patients over 60 years of age. Unlike many other types of heart disease, rheumatic heart disease is not a problem of great importance among persons past middle age.

Rheumatic fever, Sydenham's chorea and rheumatic heart disease are relatively uncommon under 5 years of age. Very few cases of rheumatic fever under age 2 were admitted, and comparatively few previous histories indicated the onset of rheumatic infection in infancy.

Approximately the same number of males as females were admitted for rheumatic fever; slightly more females than males gave histories of rheumatic fever. The distribution of rheumatic heart disease according to sex indicated a slightly greater percentage of females. Sydenham's chorea was nearly twice as common among females.

Rheumatic fever and rheumatic heart disease were less common among negroes than might be expected, considering their unfavorable economic circumstances as a result of which they are more likely to be hospitalized. A considerably greater percentage of first attacks of rheumatic fever was indicated among colored persons

in the 20 to 39 year age period. Sydenham's chorea was relatively uncommon among negroes. The possibility is suggested that rheumatic heart disease is more likely to develop in association with chorea among colored persons.

The clinical records of 63.3 per cent of 1,324 cases of rheumatic fever indicated diagnoses of rheumatic heart disease. The percentage of rheumatic fever with heart disease was greatest among persons under 20 years of age.

Of the 3,654 cases of rheumatic heart disease, 61.5 per cent gave histories or exhibited clinical manifestations of rheumatic fever. Sydenham's chorea, with or without rheumatic fever, was indicated in 15.2 per cent of rheumatic heart disease. Excluding the cases of chorea which also gave histories or presented clinical evidence of rheumatic fever, 11.4 per cent of the cases of rheumatic heart disease gave histories of having had chorea without frank attacks of rheumatic fever. Altogether, 72.7 per cent of rheumatic heart disease gave histories or exhibited clinical manifestations of rheumatic fever, Sydenham's chorea or both of these conditions.

Diagnoses of rheumatic heart disease were indicated in 42.1 per cent of Sydenham's chorea. This percentage would probably have been higher had these cases been followed after discharge from hospital. These studies and the results of a number of other investigations indicate that a child with almost any form of Sydenham's chorea stands a much greater chance of developing rheumatic heart disease than a child who has never had any form of Sydenham's chorea. This, together with the fact that 10 to 15 per cent of cases of rheumatic heart disease give histories of chorea, many without frank attacks of rheumatic fever, suggests that Sydenham's chorea should continue to be regarded as a manifestation of the rheumatic state.

The importance of activity of rheumatic infection is suggested by the fact that 56.4 per cent of 3,446 cases of rheumatic heart disease uncomplicated by subacute bacterial endocarditis were regarded as presenting signs of rheumatic activity. This is probably an underestimate. Over 80 per cent of cases under age 20 were considered as having active rheumatic infection. Of the 3,654 cases of rheumatic heart disease, including subacute bacterial endocarditis when occurring as a complication, 22.9 per cent presented clinical manifestations of rheumatic arthritis. The percentage of rheumatic heart disease with rheumatic fever was greater among cases under 20 years of age.

Among 324 cases of subacute bacterial endocarditis, 64.5 per cent were regarded as superimposed on rheumatic heart disease. Comment is made on the infrequency of subacute bacterial endocarditis as a complication of cardiovascular syphilis.

Comment is made upon the discrepancy in the age distribution of clinical diagnoses of rheumatic fever in hospitals, most of which are either approved for internship by the American Medical Association or are accredited children's hospitals, and the age distribution of deaths attributed by physicians to rheumatic fever, as indicated by mortality statistics obtained from the local office of vital statistics. This suggests the inadvisability of making rheumatic fever at all ages a notifiable disease. Measures directed toward combating this problem should be concentrated on persons under 20 years of age, the period in which most cases develop.

AUTHOR.

Swift, Homer F.: Rheumatic Heart Disease. Pathogenesis and Etiology in Their Relations to Therapy and Prophylaxis. *Medicine* 19: 417, 1940.

An attempt is made to describe the manner in which cardiac and vascular damage develop as a result of rheumatic fever, and how the final picture results from either repeated insults to important tissues or from a long-continued low grade inflammatory process. Attention is directed toward the importance of functional trauma in localizing the permanent damage and scarring to certain

structures, and to the role of this functional trauma in helping to continue an inflammatory process which might subside rapidly were complete rest attainable; as a corollary, prolonged physiologic rest is indicated to keep scarring at the minimum. The factor of infection in rheumatic fever is apparently closely related to the action of group A hemolytic streptococci; hence an important element in prevention of relapses is protection from such streptococci. A consideration of these factors is necessary either in handling a rheumatic individual or in framing a larger general program. Elsewhere are presented other features of rheumatic fever, such as the probable size of the problem and environmental influences which are amenable to alteration.

AUTHOR.

**Stone, Simon:** Treatment of Sydenham's Chorea by Fever and Vitamin B Therapy. *New England J. Med.* 223: 489, 1940.

Twenty patients with severe, moderately severe, and mild cases of Sydenham's chorea were treated. Five of the seven severe cases received artificial fever therapy, together with vitamin B complex given orally and thiamin chloride given parenterally. One severe and one moderately severe case received thiamin chloride parenterally and vitamin B complex orally, while all the others received oral medication only.

In the electropyræxia-treated cases recovery was produced with about fourteen hours of fever at 104° F. or over. When this was combined with vitamin B therapy, advanced cardiac conditions were found to be no contraindication to the fever treatment. Usually a change for the better in the carditis was noted at the end of the treatment.

One of the two cases treated with thiamin chloride responded with cessation of symptoms after the second intravenous injection of 10 mg. of the drug.

Various degrees of behavior disturbances were seen in most of the moderately severe and milder cases. They all received 4 to 8 c.c. of vitamin B complex orally, three times daily. The improvement in physical manifestations was less rapid than it was in the fever-treated cases, but most of the symptoms disappeared within one month. No hospitalization was required for any patients in this group. Improvement was noted in their behavior concomitantly with the change for the better in choreic manifestations.

AUTHOR.

**Perry, C. Bruce:** Rheumatic Heart Disease in Identical Twins. *Arch. Dis. Childhood.* 15: 177, 1940.

Two pairs of apparently identical twins are described. In the first both children suffered a similar rheumatic attack following a sore throat, which in only one produced scarlet fever. In the second, only one child developed acute rheumatism and carditis although they had been brought up together. It is concluded that while heredity is of considerable importance in the causation of acute rheumatism, another factor, probably infection, plays an equally, if not more, important role.

AUTHOR.

**Prinzmetal, Myron, Lewis, Harvey A., and Leo, Sidney D.:** The Etiology of Hypertension Due to Complete Renal Ischemia. *Clin. Sc.* 72: 763, 1940.

Perfusates of totally ischemic kidneys of cats contain a pressor substance which is not present in the perfusates of normal kidneys, ischemic hind limbs, or ischemic gravid uteri.

The pressor material in ischemic renal perfusates originates directly in the kidney as a result of complete ischemia.

The pressor principle contained in ischemic renal perfusates is the cause of the hypertension which follows the re-establishment of circulation in completely ischemic kidneys, since perfusates of unreleased completely ischemic kidneys contain more pressor material than perfusates of released ischemic kidneys of the same animal.

The pressor principle in ischemic renal perfusates is presumed to be renin for the following reasons: a) Both substances are destroyed by boiling. b) Both substances induce tachyphylaxis. c) The configuration of both pressor curves is identical. d) The pressor action of both is not reversed by 933F, proving they are not epinephrine-like substances. e) When incubated with plasma, both form a heat-stable pressor substance. f) The pressor effect of both is uninfluenced by a previous injection of cocaine. g) Unreleased, completely ischemic kidneys yield more pressor material on extraction than do released ischemic kidneys of the same animal.

The perfusates of blood-free ischemic kidneys contain more renin than those of blood-filled ischemic kidneys.

A method is described by which the power of various substances to inhibit or enhance the production of renin in the ischemic kidney may be tested.

A small amount of the heat-stable pressor substance, presumably angiotonin or hypertensin, is formed by the reaction of the pressor material (renin) and plasma in the vessels of the kidney during the period of complete ischemia.

AUTHORS.

Muñoz, J. M., Braun-Menéndez, E., Fasciolo, J., and LeLoir, L. F.: The Mechanism of Renal Hypertension. *Am. J. M. Sc.* 200: 608, 1940.

The ischemic kidney secretes renin. This substance is an enzyme which acts on a blood globulin ("hypertensin precursor") and gives rise to a substance ("hypertensin") which has a direct vasoconstrictor action. Another enzyme, "hypertensinase," which destroys hypertensin is present in blood and tissues.

Hypertensin has been found in the blood of ischemic kidneys and can also be prepared in vitro by incubating renin with blood globulins. Some chemical and pharmacologic properties of hypertensin have been studied.

Methods are described for the estimation of renin, hypertensin precursor, and hypertensinase in blood.

After injection of renin into chloralosed dogs, the hypertensin precursor decreases and even disappears from the blood. After nephrectomy, the hypertensin precursor increases and hypertensinase decreases.

AUTHORS.

Simon, Morris A.: The Nephrotic Syndrome With Hypertension in Diabetes Mellitus. *Canad. M. A. J.* 43: 425, 1940.

In older patients with diabetes of long standing, a nephrotic syndrome (massive edema of nephrotic distribution, hypoproteinemia, hypoalbuminemia, lowering of the albumin-globulin ratio, and massive albuminuria) may supervene, which is accompanied by hypertension and a variable degree of renal failure.

The kidneys of such persons show a characteristic and distinctive glomerular and arteriolar degenerative change which indicates that one is dealing with a distinct clinicopathologic entity.

Two cases which fulfill the clinical and pathologic criteria of this disease entity have been reported.

AUTHOR.

Fischer, Robert: Clinical Investigation Concerning the Jugular Venous Pulse. *Cardiologia* 4: 267, 1940.

The c-waves of the jugular vein pulse tracing are bigger in auricular fibrillation than in normal rhythm; the systolic decrease disappears if cardiac congestion develops. Typical changes of the jugular pulse can be observed in cases of tri-



cuspidal insufficiency with auricular fibrillation. The jugular vein pulse does not show typical changes in any other valvular disease; however, it reveals conditions of cardiac failure and of the venous side of the peripheral circulation.

AUTHOR.

**Parsons, Leonard G., and Ebbs, J. H.: Generalized Angiomatosis Presenting the Clinical Characteristics of Storage Reticulosis. Arch. Dis. Childhood. 15: 129, 1940.**

4

A clinical and pathologic report is given of a 14-year-old girl who showed clinical evidence of the "osseous form of Gaucher's disease" but who at post-mortem examination was found to have suffered from cavernous angiomata varying in size in the liver, spleen, retroperitoneal glands, thymus, mediastinum, lungs, pleura, kidneys and most of the bones of the body. The case is a difficult one to classify because of the widespread involvement of reticuloendothelial tissue, although histologically it is apparently an example of multiple hemangiomata, the cells of which have benign histologic characters. A discussion of the relation of this condition to "reticulosis" and "reticuloendotheliosis" is included.

AUTHORS.

**Grant, R. T.: Observations on Periarteritis Nodosa. Clin. Sc. 4: 244, 1940.**

A series of seven cases of periarteritis nodosa is described.

The chief pathologic and clinical features of the disease are discussed.

The evidence suggests that periarteritis nodosa is much less rare than is commonly thought, that it is not necessarily or even usually fatal, and that it can be recognized at the bedside in a considerable proportion of cases.

AUTHOR.

**Smith, Fred M.: Concerning the Correlation of the Pathology and Symptoms of Coronary Artery Disease. Ann. Int. Med. 14: 65, 1940.**

In coronary artery disease the changes in the arteries are the only constant feature. The response of the heart in any particular instance is no doubt influenced by many factors, but the ability to maintain an adequate circulation to the myocardium through the development of collateral circulation is perhaps the most important. Clinical and experimental studies have demonstrated that this is more effectively accomplished if there is a gradual occlusion of the vessels. In the normal subject the communications between adjacent vessels are limited and in most instances are made by means of the smaller vessels. Therefore, the abrupt closure of one of the main vessels early in the course of the disease usually results in a large area of infarction. If, on the other hand, the obstructive process develops slowly and is not terminated too soon by a thrombus, there may be very little or perhaps no significant degeneration of the myocardium. Thus, the rate of the formation of the obstruction determines in a large measure the extent of the collateral circulation, the histologic changes in the myocardium, the efficiency of the heart, and quite probably the character of the clinical expression.

Of the various symptoms pain is the most difficult to explain. Most workers in this field believe that insufficiency in the coronary circulation is the basic factor. Two features in particular, however, are difficult to explain on this hypothesis. In the first place, there is an occasional case in which there is no demonstrable disease of the coronary arteries or in which, if disease is present, it is regarded as insignificant. Moreover, many with advanced disease of the coronary arteries never have angina pectoris. In the former the angina is usually associated with conditions which

impose excessive demands on the heart. There is also the possibility that increased vasomotor tone or spasm may be a factor. Finally, in the cases of extensive disease of the coronary arteries, the receptive state of the sensory nerve endings, or perhaps of the nervous mechanism in general, may determine the presence or absence of pain.

AUTHOR.

**Carere-Comes, O., and Canna, S.: The Musculature of the Veins at Varying Ages. Quantitative Histological Research. *Cardiologia* 4: 283, 1940.**

Using a quantitative-histologic method, the authors have examined morphologically and quantitatively the senile variations in the muscle of the walls of various veins (femoralis, saphena magna, oneralis, mediana basilica, jugularis interna, cava inferior) of each of thirty-eight corpses.

The structural and quantitative similarities and differences in the vein muscle in relation to the regions explored are described.

The changes in the various muscle sheaths due to old age, together with the appearance of the senile atrophy of the vein muscle, are noted.

The sex difference in the vein muscle is pointed out.

The possible functional importance of the place variations and senile changes in the veins, the clearly functional relations between skeleton and vein muscle, and the similarity of the changes in the vein muscle with those changes in tonus and the venous pressure described by other authors are considered.

AUTHORS.

**Asmussen, Erling, Christensen, E. Hohwü, and Nielsen, Marius: The Regulation of Circulation in Different Postures. *Surgery* 8: 604, 1940.**

Our experiments indicate that the circulation rate in quiet standing is on the lower limit of which is really desirable and that, even if the fast pulse rate in the standing position in itself is no sign of insufficiency, it indicates on the other hand that some extra stress is put onto the pressure-regulating mechanism.

A diminished cardiac output during quiet standing has to be looked upon as a sign of insufficiency, even if the  $O_2$  consumption and the arterial blood pressure remain normal. The vessels of the lower extremities are distended by hydrostatic forces; a large amount of blood remains there and consequently the filling and pressure of the central veins get too low to secure an adequate filling of the heart and a normal cardiac output. Through an increased heart rate and through compensatory contractions of the vessels in certain organs (e.g., in the intestines) a normal arterial blood pressure might be obtained. However, it must be remembered that a diminished circulation rate to these organs with partly contracted vessels locally may have an unfavorable effect. It may be of great importance that circulatory insufficiency due to a peripheral dilation of the vessels or to a loss of blood can be counteracted by an elevation of the lower extremities. The auto-transfusion of blood that can be made in this way may be of great significance. In cases where a circulatory insufficiency due to a disproportion between the total blood volume and the capacity of the vessels is obvious, any posture where hydrostatic forces can induce an increased filling of the vessels of the lower extremities should be avoided. Even a small decrease in cardiac output may mean a rather severe insufficiency of the circulation of certain organs. The beneficial effect of the reclining position to a great extent may be due to the abundant blood supply to the different organs obtainable in that position.

AUTHORS.

White, Paul D.: Pulmonary Embolism and Heart Disease. A Review of 20 Years Experience. *Am. J. Med. Sc.* 200: 577, 1940.

Pulmonary embolism has failed surprisingly to attract the interest and attention it has deserved from general practitioners and those working primarily in the field of internal medicine, in contrast to its long-standing recognition by surgeons and obstetricians as a serious complication after operation, accident, or childbirth. It needs emphasis as a medical disease because of its frequency and importance in nonsurgical and nonobstetric cases.

About one-third of the cases studied simulated heart disease and the remainder complicated it. Of the former (28 in number), one-half (14) showed the signs of acute cor pulmonale, including characteristic electrocardiographic abnormalities. In most cases pulmonary embolism is either so mild or so rapidly fatal that such signs are not present or the patients are examined only after the height of the effect of the pulmonary arterial obstruction has passed.

Pulmonary embolism and infarction are easily overlooked, especially in the presence of congestive heart failure, when they are most common; or they are erroneously diagnosed as something else, especially pneumonia, congestive heart failure, or coronary thrombosis.

Clues to the diagnosis lie in the occurrence of unexplained fever, leucocytosis, tachycardia, faintness, prostration, dyspnea, or even jaundice (from hemolysis of the infarct plus an engorged liver), especially in a cardiac patient with heart disease (and particularly in the presence of mitral stenosis or heart failure).

AUTHOR.

Allan, Warde B., and McCracken, Joseph P.: Aneurysm of the Pulmonary Arteries. *Am. J. Syph., Gonorr. & Ven. Dis.* 24: 563, 1940.

Two cases of aneurysm of the pulmonary artery due to syphilis are reported, one of which is established; the findings in the second case are suggestive. The significant features are summarized, but no definite criteria for recognizing this condition are evident.

AUTHORS.

Nichols, Charles F., Ostrum, Herman W., and Widmann, Bernard P.: Aneurysms of the Ascending Aorta, Aortic Arch and Innominate Artery. A Clinical, Anatomical and Roentgenological Study. *Am. J. Roentgenol.* 43: 845, 1940.

Many articles dealing with aneurysms have been published but only a very limited number have been accompanied by anatomic studies. We have attempted in this presentation to emphasize the anatomic relation of the aorta and to show how a knowledge of this, as detailed in the accompanying illustrations, may serve to clarify and simplify the subject. Not only will this detailed anatomic relation be valuable in the diagnosis of aneurysms but it will also greatly aid in a differential diagnosis of all space-taking lesions which occur in the thorax, adjacent to the heart.

AUTHORS.

Brown, Samuel, McCarthy, J. E., and Fine, Archie: Cardiovascular Dynamics. *Radiology* 35: 290, 1940.

The historical development of roentgenkymography is briefly reviewed. The principle and technique are described. The physiologic processes related to movement of the cardiovascular dynamics under normal and abnormal conditions are discussed in more or less detail. It is concluded that roentgenkymography provides a perma-

ment record of roentgenoscopic observation. It is rarely of direct aid in diagnosis, but helps confirm the roentgenoscopic and roentgenographic findings.

AUTHORS.

**Levin, Elias:** Action of Coramine on Blood Volume in Cardiac Compensation and Decompensation. *Rev. argent. de cardiol.* 7: 146, 1940.

The circulating blood volume was determined in seven cardiac patients before and after intravenous injections of coramine. Three of the four compensated cardiac patients showed no change, while those with cardiac decompensation showed a reduction in blood volume. Only two patients, one decompensated and another compensated, reacted to the injection of coramine with an increase in blood volume, but in both cases the initial volume was smaller than normal.

Basing his conclusion on these results, the author concludes that the action of coramine depends on the existent circulatory blood volume; if it is increased, coramine will reduce it, and vice versa.

The mechanisms of these actions are probably different; while the increase of blood volume is mediated through peripheral vascular mechanism, its decrease is probably due to cardiac action.

AUTHOR.

**Stroud, William D., and Twaddle, Paul H.:** Observations Upon the Effect of Coramine in Certain Cardiac States. *Ann. Int. Med.* 14: 361, 1940.

It has been demonstrated that coramine may have a beneficial action on the abnormal respirations associated with cardiac disease. Dramatic responses, however, are not usually found from oral doses, but rather a slow progressive improvement—usually one to three days elapse before the optimum benefit is realized. A more prompt but transient response follows its use intravenously and may be attended (as used in 5 c.c. doses) by symptoms from widespread cerebral stimulation.

Cardiac efficiency was not shown to be constantly improved from prolonged oral use of coramine.

Decline in intrathecal pressure, following its intravenous administration, was observed and, to a less constant or striking degree, a decline in venous pressure. That these pressure changes are directly related to the improvement noted is considered doubtful. The present evidence points to coramine's stimulation, as a chemical agent, of the respiratory receptors, either peripherally or centrally.

Further studies are indicated.

AUTHORS.

**Allen, C. R., Stutzman, J. W., and Meek, W. J.:** The Production of Ventricular Tachycardia by Adrenalin in Cyclopropane Anesthesia. *Anesthesiology* 1: 158, 1940.

At least one action of cyclopropane is to render the dog's heart more irritable to adrenalin by direct stimulation of a brain center above the pons which sends impulses to the heart by way of the sympathetic nerves. The direct action of adrenalin on the heart thus sensitized produces ventricular tachycardia.

AUTHORS.

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THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is \$5.00 a year and journal membership at \$10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

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## Original Communications

### A PRELIMINARY INVESTIGATION OF THE THERAPEUTIC VALUE OF LANATOSIDE C (DIGILANID C)

GEORGE FAHR, M.D., AND JOHN LADUE, M.D.  
MINNEAPOLIS, MINN.

TWO hundred fifty-six patients with heart disease who have been admitted to the Minneapolis General Hospital since October, 1937, and treated with the recently isolated, crystalline, stable glycoside, lanatoside C (Digilanid C)\* have exhibited rapid and efficient clinical responses. In cases of auricular fibrillation, a dramatic slowing of the heart rate was frequently observed a few minutes after intravenous administration of the drug; cardiac failure in the presence of normal sinus rhythm disappeared more rapidly than in a control series in which no digitalis was given; some hyperthyroid patients with auricular fibrillation responded promptly with a slowing of the heart rate; and, in a relatively high percentage of cases, cardiac arrhythmias were quickly replaced by normal sinus rhythm. Toxic reactions were rare, and a few patients who had been unable to tolerate digitalis took lanatoside C with a good therapeutic result.

Our results indicate that this drug should now have a wide clinical trial, so that we may be fully informed as to its advantages over the usually employed purpurea preparations.

Digitalis lanata contains a glycoside, lanatoside C, which has no chemical relationship with the glycosides of digitalis purpurea. It occurs exclusively in the digitalis lanata species and is chemically marked by the structure of its aglucone digoxigenin, which, as has been shown by Smith,<sup>1</sup> differs considerably from the genins of the other glycosides which are derived from digitalis lanata and purpurea. However, the exact relationship between these two digitalis plants was not understood until the publication of the exhaustive studies of Stoll,<sup>2</sup> which resulted

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\*The Committee on Nomenclature of the Council on Pharmacy and Chemistry of the A. M. A. recently accepted the terms lanatoside A, lanatoside B, and lanatoside C as scientific (nonproprietary) names for the three cardioactive glycosides isolated from the leaves of digitalis lanata. In the early clinical literature lanatoside C is referred to as Digilanid C.

in the isolation of all of the cardioactive glycosides of *digitalis lanata* and *purpurea*, together with the products of their enzymatic hydrolysis.

The digitalis glycosides consist of an aglycone or genin nucleus, linked by a side chain to a variable number of sugars. The aglycones have been designated as the carriers of the cardioactive properties, but, when deprived of their sugars, they are practically insoluble in water, scarcely absorbable, and devoid of fixation power. It may thus be assumed that the therapeutic properties of a cardioactive glycoside are to a certain extent determined by the sugars which are linked to the aglycone. The lanatosides A, B, and C comply with this idea because they are crystalline, stable, adequately soluble glycosides of high carbohydrate content.

Because lanatoside C is a crystalline substance, biologic assay is not necessary, and its dosage may be determined gravimetrically, rather than by the "cat unit" method, once the therapeutic efficacy is established. Since it is a chemically pure substance which contains no enzymes, lanatoside C is not subject to changes in potency over a period of years, as are galenic preparations.

In 1938, Moe and Visseher<sup>3</sup> completed a pharmacologic study of lanatoside C. This work showed that lanatoside C is a drug which greatly increases the mechanical efficiency of the failing heart, and, at the same time, has the highest ratio of therapeutic to toxic effect of any of the cardioactive glycosides which they investigated. Moreover, Essex, Herrick, and Visseher,<sup>4</sup> in 1938, demonstrated that lanatoside C, in therapeutic doses, did not reduce the flow of blood through the coronary arteries of the dog. From a study of Visseher and Moe's and Visseher, Herrick, and Essex's work, we came to the conclusion that lanatoside C would probably be a useful drug in the treatment of heart failure and determined to make an extensive study of its therapeutic effect on patients.

Bauer,<sup>5</sup> Hu, Lien, and Li,<sup>6</sup> and Büchner<sup>7</sup> have shown that digitoxin, the most toxic glycoside of *digitalis purpurea*, when administered in large doses, will cause degenerative changes in the heart muscle of dogs within thirty days. The doses used were far in excess of those given clinically, but their results suggest that degenerative changes may be produced by digitalis glycosides. Hence, we thought it advisable to conduct similar experiments with lanatoside C.

We gave large quantities of lanatoside C (as much as five times the therapeutic dose) daily, to dogs, over periods of one to three months. One 32-pound dog received 1.25 mg. of the drug by mouth daily for three months, which is equivalent to 6.75 mg., or 25 cat units, daily for a 160-pound man. An exceedingly careful histologic examination of this dog's myocardium by Dr. Clawson, of the Department of Pathology, together

with Dr. LaDue, revealed no abnormalities. Another dog, which was given 1.5 c.c. (0.3 mg.) intravenously every day for thirty days, was also found to have a histologically normal heart muscle. This is equivalent to the amount given intravenously for complete digitalization in man and would never be given daily.

These experiments are being repeated with larger doses, but we have sufficient data at the present time to conclude that it is highly probable that lanatoside C can be given in therapeutic doses to man over long periods of time without danger of producing morphologic changes in the myocardium.

Lanatoside C was supplied by the Sandoz Chemical Works, Inc., in tablet form, and in ampules for intravenous use. Each tablet contained 0.25 mg. of lanatoside C,\* and each cubic centimeter of solution, 0.20 mg. of the drug. According to Rothlin<sup>8</sup> and Visseher,<sup>9</sup> 0.28 mg. of the drug is equivalent to an international Magnus-DeLind unit.

#### METHOD OF INVESTIGATION

Clinicians agree that digitalis is efficient in the treatment of heart failure accompanied by auricular fibrillation. For the physician who practices without the aid of venous pressure and vital capacity measurements, the slowing of the heart rate following the administration of a digitalis preparation in cases of auricular fibrillation is considered one of the most reliable indications of therapeutic response.

For this reason, we began our study by selecting only patients with auricular fibrillation and heart rates above 120 who had not taken any digitalis preparation for at least three weeks. The amount of lanatoside C needed to stabilize the heart rates of these patients below 85 determined the so-called "digitalizing dose" which we now use in all cases of heart failure and in certain arrhythmias.

Reports on lanatoside C,<sup>10</sup> to date, say nothing of a "digitalizing dose," but advise giving two to eight tablets a day, or, for patients with severe heart failure, 2 to 4 c.c. intravenously. Although no average rate of action has been given, the case reports of previous investigators show a much slower response (from two to ten days for a decline in pulse rate, etc.) than we have obtained.

Individual records were kept on all of our patients. On admission, the heart rate was counted at the apex for one full minute, and again every two hours thereafter until it fell to 85, or below. The venous pressure and vital capacity were measured at the same time, and at least once daily throughout the period of cardiac failure. A daily chart recorded these measurements, the fluid intake and output, the degree of dyspnea, orthopnea, and cyanosis, and the variations in peripheral and pulmonary edema, as well as hepatic enlargement, together with clinical notes concerning the subjective state of the patient. No diuretics or other drugs were given, except sedatives, usually morphine or phenobarbital, as needed to secure rest or relief from cough or pain. Only when collections of fluid in the serous cavities threatened the life of the patient was salyrgan given or a paracentesis done. The fluid intake was limited to 800 c.c. a day. Urinalyses, and blood and serologic studies were ordered routinely; teleoroentgenograms were taken on admission and discharge, and electrocardiograms were made frequently. Thus, a quantitative, as well as a qualitative, measure of the day-by-day cardiac status of each patient was secured.

\*Lanatoside C (Cedilanid, Sandoz Chemical Works, Inc.) is now put up in tablets containing 0.5 mg.



## USE IN THE PRESENCE OF AURICULAR FIBRILLATION

To date, 102 patients with auricular fibrillation\* have received lanatoside C. It must be emphasized that there was no selection of cases; patients were treated regardless of age, sex, type of heart disease, or severity of heart failure, except that patients with coronary thrombosis and patients who had been taking therapeutic doses of digitalis were excluded.

Lanatoside C was first given in doses of one tablet (0.25 mg.) four times a day until the pulse rate fell to 85, or below. These early patients required eight to forty-eight tablets to slow the pulse rate within two to twelve days. Larger doses were therefore given, and the digitalizing amount best suited to the majority of patients was found to be an initial dose of fifteen tablets, followed within twelve to twenty-four hours by ten additional tablets, given in single or divided doses. The exact relation of dosage to weight has not yet been ascertained, but women usually require slightly less lanatoside C for maintenance than men.

AURICULAR FIBRILLATION.  
WITH INTRAVENOUS LANATOSIDE C

TIME.	PULSES.						
	>150	150-140	140-130	130-120	120-100	100-90	<90
0-30 MIN.	•	•	••	••	••	•	
30-60 MIN.	••	••	•••		•		
1-2 HRS.	••••	•••••	••••	•••••	•		•
2-3 "	•		•				
3-5 "		•	•	•			
5-12 "	•	•					
12-24 "			•	•	•		
24-48 "	•			•	•		
48-72 "							
3-7 DAYS.			•	•	•	•	
7+ DAYS.							
TOTALS.	11	13	16	12	7	2	1

Fig. 1.—This table shows the time required, after the intravenous administration of lanatoside C, for the heart rate to fall to 85, or lower. The circles represent patients who died at varying intervals after the administration of the drug and the decline in heart rate. Cases in which the heart rate was originally less than 100 have no significance with respect to the time at which the fall in heart rate to 85, or below, occurred.

After several months' experience with the oral preparation, intravenous administration was begun. Ampules containing 0.2 mg. of lanatoside C per cubic centimeter were obtained, and an attempt was

\*Cases of paroxysmal auricular fibrillation were not included, nor were cases of auricular fibrillation associated with hyperthyroidism.

made to give the "digitalizing dose" in one injection. Trials of 2, 4, 6, and 8 c.c. injections were made before a dose of 8 c.c. was chosen as the optimal digitalizing dose for adults.

Fig. 1 shows the rapidity with which the heart rates of fifty-two patients fell to 85, or lower, when 8 c.c. of lanatoside C were given intravenously. Thirty-eight patients responded with a slowing of the pulse rate to 85 (or lower) in less than two hours. Two required twelve to twenty-four hours; two, twenty-four to forty-eight hours; and two, forty-eight to seventy-two hours. These intervals were longer than may actually be expected, for twenty patients who were classified as having responded within "one to two hours" had their pulse rates checked only every two hours, and some of them undoubtedly responded more promptly. A detailed study of fifteen consecutive patients whose heart rates were counted every five minutes following the injection of 8 c.c. of lanatoside C gave a more accurate index of the rapidity of the drug's action. All had heart rates of more than 120, after twenty-four to forty-eight hours of rest in bed, but slowing of the pulse rate to 85, or less, occurred within two to ninety minutes, with a mean time of thirty minutes, after the administration of the drug.

AURICULAR FIBRILLATION, WITH ORAL LANATOSIDE C					
TIME.	PULSES.				
	>140	140-120	120-100	100-90	<90
0-30 MIN.					●●●●●
30-60 MIN.				●	
1-2 HRS.			●		
2-3 "					
3-5 "					
5-12 "			●		
12-24 "	●●	●●●	●● ●●	1	
24-48 "	●	●●● ●●	●●● ●	●●	
48-72 "		●● ●	●		
3-7 DAYS.	●		●		
7+ DAYS.					
TOTALS.	4	11	10	3	12

Fig. 2.—This shows the time required, after the oral administration of lanatoside C, for the heart rate to fall to 85 per minute, or lower. The circles represent patients who died at varying intervals after the decline in pulse rate. The first horizontal column indicates what the heart rates were at the time of administration of the drug. Patients whose heart rates were originally less than 100 are included, but the data in these cases have no significance with respect to the time at which the fall in heart rate to 85, or lower, occurred.

The response of patients with auricular fibrillation to the oral administration of lanatoside C is also more rapid than the average time indicated in Fig. 2, since the results in twenty-five early cases, in which

insufficient digitalizing doses were given, are included. Two of these early cases appear in the three- to seven-day group, three in the forty-eight- to seventy-two-hour group, six in the twenty-four- to forty-eight-hour group, and one falls in the twelve- to twenty-four-hour group. All patients who received twenty-five tablets of lanatoside C within twenty-four hours responded with a slowing of the pulse rate within forty-eight hours after the administration of the first dose. In more than half of these cases the slowing occurred within twenty-four hours.

When given intravenously, lanatoside C's rapidity of action may be compared to that of strophanthin, and, when administered by mouth, it acts as fast as any oral preparation of *digitalis purpurea*.

We have given lanatoside C to twelve patients with auricular fibrillation whose heart rates were less than 90. In two cases the venous pressure was above 15 cm. of saline and fell to normal three days after 8 c.c. of lanatoside C were given intravenously. Six patients received twenty-five tablets (6.25 mg.) during a twenty-four-hour period; two with venous pressures of 15 cm. recovered from their heart failure within a week; three had left-sided heart failure which rapidly disappeared. Smaller doses of lanatoside C (five to twenty tablets) were given orally to three patients with venous pressures greater than 20 cm. of saline, with favorable results. All received maintenance doses of one to five tablets a day. None of these patients exhibited signs of over-digitalization, and all showed marked improvement after receiving lanatoside C.

#### MAINTENANCE DOSE

It is desirable to know the maintenance dose of lanatoside C when the heart rate in cases of auricular fibrillation has dropped to about 80. We found that when the heart rate prior to treatment was very rapid and the venous pressure high, five tablets (1.25 mg., or 4.5 cat units) were usually required daily during the period of congestive failure. In two instances, it was necessary to give ten tablets a day. Once good compensation was established, however, doses of this magnitude occasionally brought about symptoms of over-digitalization, such as nausea, vomiting, and numerous extrasystoles, although these were not at all common. When such symptoms did appear, the administration of the drug was discontinued for two days, after which a daily dose of one to three tablets kept the pulse rate between 60 and 70.

For example, O. N., a 56-year-old man with advanced mitral heart disease, auricular fibrillation (rate 140), and severe congestive failure (venous pressure, 28) required 2.5 mg. (ten tablets) of lanatoside C daily during the nineteen days his venous pressure remained above 19. Smaller doses resulted in a heart rate of 100 or more, increased dyspnea, orthopnea, etc., but, when the 2.5 mg. dosage was continued for three days after the venous pressure had fallen to 8, the patient complained of nausea, emesis, and palpitation, and numerous extrasystoles were heard.

Administration of lanatoside C was discontinued for two days, and then a daily dose of two tablets kept the pulse rate between 60 and 70 and permitted moderate activity.

#### DURATION OF ACTION OF LANATOSIDE C

How quickly is lanatoside C destroyed in the body? No chemical means has yet been devised to solve this problem. On the other hand, the heart rate of patients with auricular fibrillation offers a reasonably reliable method of checking the drug's duration of action. Seventeen patients with heart rates of more than 120 were given lanatoside C until the rate fell to 80, or lower. The drug was then withheld, and the heart and radial pulse rates were checked daily until they rose above 90. The acceleration occurred within seven to twenty-one days, with a mean of twelve days. This variability (seven to twenty-one) can probably be explained in part by the fact that in the presence of severe congestive failure the escape of the pulse occurs more rapidly. This approximates the results reported by Robinson<sup>11</sup> for digitalis purpurea.

#### NORMAL SINUS RHYTHM

THERAPY	TOTAL NO. OF CASES	AV. NO. OF DAYS FOR VENOUS PRESSURE TO FALL TO 8 CM. WATER	AV. NO. OF DAYS FOR ONSET OF DIURESIS	AV. NO. OF DAYS FOR SIGNIF. RISE —30%— IN VITAL CAPACITY	AV. NO. OF DAYS IN BED	AV. NO. OF DAYS IN HOSPITAL	MORTALITY %
<i>Venous Pressure &gt; 15 Cm. of Water</i>							
Control	24	14.8(14)	6.4(12)	13.0(11)	24.1(12)	27.4(13)	41.7
Lanatoside C	54	4.5(39)	3.3(31)	8.5(32)	12.2(33)	19.5(27)	25.9
<i>Venous Pressure &lt; 15 Cm. of Water</i>							
Control	18	3.7(12)	3.3(11)	11.6(9)	10.3(12)	18.4(14)	22.2
Lanatoside C	11	2.1(10)	3.0(6)	6.2(6)	11.4(11)	18.8(11)	0.0
<i>Lanatoside Delayed</i>							
Control period	21	>17.1(16)	>17.1(16)	>17.1(16)			
After lanatoside	21	3.1(16)	3.0(13)	7.3(11)	10.4(13)	19.7(12)	23.8
VENOUS PRESSURE      AURICULAR FIBRILLATION							
>15 cm. of water	67	3.4(47)	2.3(38)	8.0(40)	15.6(34)	25.7(30)	22.4
<15 cm. of water	35	2.8(8)	2.3(13)	10.5(13)	15.2(24)	23.9(21)	11.4

Fig. 3.—This table summarizes the data on which a statistical analysis of the cases of normal sinus rhythm and auricular fibrillation was based. Numbers within parentheses indicate the total number of cases from which each average used in the statistical analysis was obtained. The average number of days is reckoned from the time of admission to the hospital in all cases except in the "lanatoside delayed" series. In the latter, the average number of days is computed from the time the administration of the drug was begun. Patients received the drug within twelve to twenty-four hours after their admission to the hospital, except in the "lanatoside delayed" series, and as noted in the text.

Patients with auricular fibrillation who received lanatoside C were usually given 1.5 grains of digitalis leaves\* as a maintenance dose before

\*Standardized according to the U. S. Pharmacopoeia X.

leaving the hospital. In no instance did evidence of under-digitalization appear within a period of two or three weeks.

Fig. 3 records the average number of days needed for venous pressures and vital capacities to come within normal ranges, the day on which diuresis appeared, and the duration of hospitalization.

It was most interesting to study the response to lanatoside C of patients with auricular fibrillation who had venous pressures greater than 15 cm. of water. The venous pressure required an average of four days to reach normal, whereas the pulse rate fell to 80, or less, much more rapidly (within two hours when the drug was given intravenously, and twenty-four to forty-eight hours after oral administration). Similarly, the onset of diuresis lagged behind the fall in heart rate, requiring an average of three days; the vital capacity took six days to rise 30 per cent. If we compare in the same table the average number of days required to lower the venous pressure of patients with normal sinus rhythm, we find that the values are approximately the same. In other words, although the pulse rates indicate that there was an excellent digitalis response within a few hours after giving lanatoside C, the objective signs of congestive failure disappeared only a little faster when the patients had auricular fibrillation than when they had normal sinus rhythm. This is indirect proof that, if the drug is effective in relieving cardiac failure with auricular fibrillation, it is nearly as effective when the heart failure is associated with normal sinus rhythm.

#### USE IN CARDIAC FAILURE IN THE PRESENCE OF NORMAL SINUS RHYTHM

MacKenzie<sup>12</sup> and Lewis<sup>13</sup> have been skeptical as to the value of digitalis in the treatment of heart failure which is not associated with auricular fibrillation, although enthusiastic about its efficacy when the heart failure is associated with auricular fibrillation. They ascribe the improvement in the circulation to the slowing of the pulse rate. Many physicians have agreed with MacKenzie and Lewis, but others, led in this country by Christian,<sup>14</sup> have insisted that digitalis is almost as effective in the presence of normal sinus rhythm.

Peters and Visseher<sup>15</sup> and Moe and Visseher,<sup>3</sup> working with the isolated heart-lung preparation, have demonstrated beyond doubt that digitalis increases the mechanical efficiency of the failing animal heart tremendously. Anitschkow and Trendelenburg<sup>16</sup> found that strophanthin reduces the elevated venous pressure and increases cardiac output in animals with failing hearts, and Cohn and Steele<sup>17</sup> have shown that digitan has the same effect. As far as we know, there has been no clinical investigation which has demonstrated scientifically that digitalis glycosides are efficacious in the treatment of congestive heart failure associated with normal sinus rhythm.

We determined to investigate this problem by dividing cases of heart failure not associated with auricular fibrillation into two series, the cases for each series to be selected alternately. Patients in the first, or control, series were kept in bed, their fluid intake was restricted to 800 c.c. per twenty-four hours, and they received sedatives as needed, but no other medication; those in the second series were given the same treatment, with the addition of lanatoside C. There were sixty-five cases in the lanatoside series and sixty-three cases in the control series. The one deviation from the rule of alternating cases came about through the insistence of an attending physician that a patient with severe heart failure receive lanatoside C despite the fact that this patient was to have been put in the control series. Rheumatic valvular lesions, hypertension, coronary arteriosclerosis, and syphilitic heart disease were among the causes of the heart failure in these cases. Patients with heart failure caused by vitamin B deficiency and hyperthyroidism were excluded. With but few exceptions, these patients were victims of long-standing heart disease who had been treated in this hospital on one or many occasions; all had severe congestive failure and presented difficult therapeutic problems.

Lanatoside C was given in the same dose that had been used for patients with auricular fibrillation. It was planned to make daily measurements of venous pressure and vital capacity on all of the patients in each series, and this was usually carried out, but, occasionally, a resident physician failed to notify Dr. LaDue that a patient had been admitted and assigned to one or the other series, as a consequence of which daily measurements of venous pressure were not made on two patients in each series.

Elevation of venous pressure is, in our opinion, the most accurate quantitative measure of right-sided heart failure; 8 cm. of 2 per cent sodium citrate solution was regarded as normal.

The first vertical column in Fig. 3 summarizes our observations in forty-two cases in the control series and forty-nine in the lanatoside C series. There were actually sixty-three cases of heart failure in the control series and sixty-five cases in the lanatoside C series, but nineteen patients who were originally in the control series and fourteen in the lanatoside series died and were not included in the statistical studies on the rate of fall in venous pressure.

Lessening of visible edema lagged behind the fall in venous pressure and was therefore a less accurate indication of the effect of treatment. On the other hand, the onset of diuresis (as noted in Fig. 3) closely paralleled the fall in venous pressure and not infrequently occurred before the latter dropped to 17 cm., the level at which the edema tendency manifests itself when the patient is up and about. Diminution of venous pressure is not the sole factor in the production

of diuresis because change in posture (bed rest) alters the effect of gravity on capillary filtration. Restriction of salt intake (not done in our cases) also tends to facilitate diuresis, but lowering of the plasma proteins, which occurs occasionally, retards its onset. Hence diuresis is a less reliable criterion of the effectiveness of the drug than are alterations in venous pressure. The time of onset of diuresis could not be ascertained in five of the control series and twelve of the lanatoside series because of incontinence.

It is impossible to measure the pressure in the pulmonary veins of man. In our opinion, the best quantitative index of changes in the degree of failure of the left ventricle is an increase or decrease in vital capacity. Vital capacity measurements were made daily, when possible. Since the close cooperation of the patient is needed in order to secure reliable vital capacity measurements, subjective factors often preclude obtaining accurate data. It was impossible to get reliable data on vital capacity in six of the control and eleven of the lanatoside series.

We found that the difference between the two series with respect to lowering of the pulse rate was not statistically significant.

The average number of days in bed and average length of hospital stay are measures of the efficacy of a drug in the treatment of heart failure, but are subject to the judgment of the physician in attendance. Usually, patients were allowed to get up seven days after the disappearance of all signs of congestive failure, unless there was some specific contraindication. One observer was responsible for these decisions (as to when the patient might get up and go home) in most of the cases. Despite these uncontrollable aspects, a glance at Fig. 3 will show that even these data showed the same trend as the unequivocal changes in venous pressure.

The "lanatoside C delayed" portion of Fig. 3 refers to twenty-one patients who were originally in the control series for an average of seventeen days, but were then given lanatoside C because they had failed to show the slightest sign of improvement; in fact, most of them were worse than when they entered the hospital, and it appeared that they were going to die. Since, in our opinion, it had not yet been proved scientifically that a digitalis glycoside is beneficial in congestive heart failure with normal sinus rhythm in man, and inasmuch as some experienced clinicians do not give digitalis in cases of heart failure associated with normal rhythm, we felt justified in withholding lanatoside C until we had proof pro or con.

Professor Treloar, head of the division of biometrics at the University of Minnesota, aided us in analyzing our results statistically, making use of the so-called "t" test for small numbers and random sampling. The cases were divided into two groups: (1) controls and treated patients with initial venous pressures greater than 15 cm. of water, and (2) con-

trols and treated patients with initial venous pressures less than 15 cm. The following statements apply only to group 1. Statistical analysis of the changes in venous pressure shows that there is a probability of less than one in ten million that the difference would arise through chance. A probability of five, or less, in 100 is ordinarily considered significant in the application of this test, although the strictest observers accept one in 100 as demonstrating that the results are not fortuitous. We can therefore state that, in our study, the average length of time required for the venous pressure to fall to 8 cm. of water was longer in the control series (14.8 days) than in the series in which lanatoside C was given (4.5 days).

Analysis of the reliability of the data concerning relative changes in vital capacity shows that there are not more than four chances in 100 that the results were accidental. That the rise in vital capacity took 100 per cent longer in our controls therefore seems significant. The differences in the rate of onset of diuresis would occur by chance only twice in a thousand times. Diuresis appeared twice as rapidly in the lanatoside C series.

Application of the statistical "t" function to the differences in the average number of days in bed (twice as long in the control series as for treated patients) shows that the probability of such an increase through chance is only one in 1,000. Patients in the control series were confined to the hospital approximately a week longer, and there are only six chances in 1,000 that this was accidental.

Because of the small number of cases, the value of the mortality statistics may be regarded as dubious. However, it is worth noting that the mortality in the control series was always higher than among the patients who received lanatoside C. Moreover, the number of deaths among our most seriously ill patients, who were originally in the control series and were eventually given lanatoside C (the "lanatoside C delayed" series), was approximately the same as among the lanatoside-treated patients who had venous pressures above 15 cm. of water and were given the drug on admission.

If we examine the figures for the "lanatoside C delayed" group in the same table, we find that the sixteen patients who survived had been in the control series for an average of seventeen days, with venous pressures above 20 cm. of water, before lanatoside C was given. Following the administration of 8 c.c. of lanatoside C intravenously, the venous pressures fell to 8 cm. of water, or less, within an average of three days, and diuresis appeared in three days in thirteen instances. Three patients were incontinent, so that it was impossible to measure their urinary output. In eleven cases the vital capacity showed a significant rise within an average of seven days, and in five the measurements were of no value because the patients were unable to cooperate.



The reader of this paper may criticize our transferring twenty-one cases that were originally in the control series to a separate group. Our answer is that we were forced to make this selection because these patients looked as if they were going to die. Even if there had not been pressure from the visiting staff and the house staff, we would have felt compelled to give these more seriously ill patients the benefit of a digitalis glycoside. The type of selection that was carried out does not in any way nullify the proof of the efficacy of lanatoside C, because these twenty-one patients were the most refractory in the control series. They showed no signs even of beginning improvement after an average of seventeen days. If these twenty-one patients had remained in the control group, there is no question that the mortality percentage would have been much higher than it was, and, if the objective signs of heart failure in these cases had ultimately receded, the average number of days required for venous pressure to fall and vital capacity to rise would have been increased significantly. The probability that these changes were the result of chance would still be less than one in ten million for the venous pressure and less than four in one hundred for vital capacity. As it is, we did not invalidate the proof of the effectiveness of lanatoside C in heart failure associated with normal sinus rhythm, but really added to the statistical proof by showing that, when lanatoside C was given in these stubborn cases of heart failure in which there had been no signs of improvement after seventeen days without the drug, the decrease in the objective signs of heart failure was as rapid as in the cases in the original lanatoside C series.

We believe that we have proved beyond doubt that lanatoside C is almost as effective in the treatment of heart failure in the presence of normal sinus rhythm as it is when the failure is associated with auricular fibrillation.

Lanatoside C was given intravenously in about 25 per cent of the cases and by mouth in 75 per cent. Although there was no statistically significant difference in the results obtained with the two methods of administration, the subjective response occurred far more quickly after intravenous injection of the drug. For example, the pulse pressure, as measured by the sphygmomanometer, and the pulse volume, as estimated by palpation, showed an almost immediate increase in many instances. The same was true of the circulation time, as measured by the sodium cyanide method. The following case history is an illustration.

A patient who had been in the control\* series for thirteen days was growing steadily worse. The venous pressure on admission was 20 cm. of water, and remained at about this level for thirteen days. On the fourteenth day, at 3:02 P.M., when 8 c.c. of lanatoside C were given intravenously, the blood pressure was 164/100; the pulse

\*This case is not included in Fig. 3. The patient came in when the statistical analysis was being made.

pressure, 64; and the cyanide circulation time, 33.5 sec. At 3:32 P.M. the blood pressure was 178/86; the pulse pressure, 92; and the cyanide circulation time, 19 sec. There was, therefore, a 44 per cent rise in pulse pressure and a 44 per cent decrease in circulation time. At 4:35 P.M. the blood pressure was 196/100; the pulse pressure, 96; and the circulation time, 20.3 sec.—a 50 per cent increase in pulse pressure and a 40 per cent decrease in circulation time. Thirty minutes after injection of the drug, roentgenkymograph studies showed a 30 per cent increase in stroke output and a 12 per cent decrease in diastolic volume. On the following day, the venous pressure was 9 cm. of water, and the circulation time, 20.4 sec.

Data on circulation time and minute volume, the latter obtained by means of the roentgenkymograph, will be reported in a later paper. This investigation, although not yet ready for publication, indicates definitely that the minute output of the heart increases within thirty minutes after the intravenous injection of 8 c.c. of lanatoside C.

#### EFFECT OF LANATOSIDE C UPON CARDIAC ARRHYTHMIAS

The re-establishment of normal cardiac rhythm in patients with auricular fibrillation of long standing who were being treated with lanatoside C has been frequent enough to be noteworthy. We have treated, over a period of years, an unusually large number of such patients with digitalis purpurea, and we regard the establishment of normal sinus rhythm in cases of nonparoxysmal auricular fibrillation as rare. Smith<sup>18</sup> states that "In our experience, digitalis rarely, if ever, has restored normal cardiac rhythm." In eight of our 102 cases of nonparoxysmal auricular fibrillation, normal sinus rhythm became established spontaneously while the patients were receiving lanatoside C.

Apparently, lanatoside C is, comparatively speaking, an effective drug in the treatment of certain cardiac arrhythmias, such as paroxysmal tachycardia of supraventricular origin, auricular flutter, and paroxysmal tachycardia caused by transient attacks of auricular fibrillation.

Five patients with paroxysmal tachycardia of supraventricular origin responded promptly to the intravenous administration of 8 c.c. of lanatoside C. Normal sinus rhythm was established within five minutes in two cases, within ten minutes in another, and within two hours in two more. The effect of carotid sinus pressure and vagus stimulation was tried in each instance before the drug was given. Comparable results were reported by Wilson and Wishart,<sup>19</sup> who gave digitalis purpurea intravenously.

In one instance of paroxysmal tachycardia of auricular origin, associated with recent coronary thrombosis, neither lanatoside C nor quinidine was effective. The patient finally died during an attack of ventricular tachycardia ten days after lanatoside C had been discontinued.\*

\*We do not give any digitalis glycosides in cases of coronary thrombosis unless 3 grains of quinidine are taken at least four times daily.

Four patients with auricular flutter were treated successfully with lanatoside C. Two of them had mitral stenosis and entered the hospital with 2:1 block and ventricular rates of 188 and 167, respectively. Both received 8 c.c. of lanatoside C intravenously, and normal sinus rhythm was restored in the first case within five minutes, and in the second within eight minutes. In neither did the mechanism pass through a stage of auricular fibrillation before normal rhythm became established.

The third patient, a young girl with congenital heart disease, had had, to our knowledge, auricular flutter for more than a year. Both digitalis and quinidine were tried without success, and she was given two tablets (0.5 mg.) of lanatoside C daily. Two months later an electrocardiogram showed that normal sinus rhythm had become established.

The fourth patient, a 76-year-old man with congestive failure caused by hypertensive and arteriosclerotic heart disease, was fully digitalized on admission and had auricular flutter with a variable block of 2:1 and 3:1. On the seventh day, 1.25 mg. of lanatoside C were substituted for digitalis purpurea and thirteen days later, the flutter changed to auricular fibrillation, with a ventricular rate of 45. Because of the slow rate, the administration of lanatoside C was discontinued and six days later, three grains of quinidine were given three times daily. The next day the pulse rate rose to 90, and two tablets (0.5 mg.) of lanatoside C, plus 9 grains of quinidine, were given. Twenty-four hours later an electrocardiogram showed normal sinus rhythm. The patient was discharged, and advised to take 9 grains of quinidine and 1.5 grains of digitalis purpurea daily, but failed to do so. Within two weeks he was readmitted; he had mild heart failure and auricular flutter (ventricular rate 150, block 2:1). The following day, 8 c.c. of lanatoside C were injected, and twenty-four hours later an electrocardiogram showed normal rhythm. He left the hospital taking 9 grains of quinidine and 1.5 grains of digitalis, but three months later returned to the dispensary with auricular fibrillation.

Another patient with auricular flutter and a 2:1, 3:1 block, who did not have heart failure, was given 8 c.c. of lanatoside C, followed by three tablets daily, and on the fourth day developed auricular fibrillation. She had been treated for auricular fibrillation for two years in the outpatient department, so that quinidine was not tried.

A 67-year-old man with coronary thrombosis came into the hospital with auricular flutter (ventricular rate 164, 2:1 block). Although it is our custom to be exceedingly cautious in administering digitalis in the presence of coronary thrombosis, we considered the rapid rate a justification for giving lanatoside C. Eight c.c. were injected without effect, and the patient died on the eighth hospital day. At autopsy, a fresh thrombus was found in the anterior descending branch of the left coronary artery, with infarction; acute pancreatitis was also noted.

A 54-year-old man with lobar pneumonia (pneumococcus, type VII), involving the entire right lung, had, in addition, auricular flutter (auricular rate 375, with 2:1, 3:1 block before the administration of antipneumococcus serum). He was given 12 c.c. of lanatoside C intravenously; the apical rate was 170 at the time of the injection. An hour later it was 64, and, after twelve hours, an electrocardiogram showed normal sinus rhythm, with a rate of 150. The patient died two hours later.

Seven patients with paroxysmal auricular fibrillation of one to four days' duration were given 8 c.c. of lanatoside C intravenously. In four, normal sinus rhythm was restored within ten minutes, and, in the remainder, within twenty-four hours. Two patients had venous pressures above 15 cm. of water; in one the pressure fell from eighteen to eight in an hour, and, in the other, from sixteen to six in one and one-half hours. It is of interest that, in two of these cases, the rhythm went through a stage of auricular flutter before becoming normal. Only one patient to whom lanatoside C was given had normal sinus rhythm on admission, and then, while taking the drug, developed auricular fibrillation. This persisted for more than nine months. If we include the seven cases of paroxysmal auricular fibrillation with the eight cases of long-standing auricular fibrillation in which normal rhythm became established, fifteen patients with auricular fibrillation developed normal sinus rhythm during treatment with lanatoside C.

#### USE IN HYPERTHYROIDISM

We believe that lanatoside C will aid the heart in hyperthyroidism by reducing both the ventricular rate (in the presence of auricular fibrillation) and the venous pressure. Some of our patients received both lanatoside C and Lugol's solution; this made it impossible to draw any conclusions. There were, however, five patients with auricular fibrillation and hyperthyroidism who did not take Lugol's solution; their pulse rates and venous pressures fell promptly after the administration of lanatoside C. The following are brief abstracts of their case histories.

CASE 1.—A 65-year-old woman with hyperthyroidism and mitral disease (no heart failure) had a basal metabolic rate of +46 per cent and auricular fibrillation, with a ventricular rate of 120. She was fully digitalized on admission but was given 8 c.c. of lanatoside C intravenously, and, within two hours, the heart rate (in the electrocardiogram) was 80.

CASE 2.—A 70-year-old housewife with mitral stenosis, hyperthyroidism (basal metabolic rate +40 per cent), and auricular fibrillation (ventricular rate 120) was given 15 c.c. of an oral preparation of lanatoside C (0.25 mg. per cubic centimeter), followed by 1.25 mg. each succeeding day for seven days; by this time the heart rate had fallen to 76, and it was maintained between 70 and 80 until she was operated on. Her basal metabolic rate ranged between +32 and +40 per cent, and her venous pressure fell from 16 cm. of water to normal. After her thyroidectomy, normal cardiac mechanism was restored by means of quinidine.

CASE 3.—A 68-year-old woman, who was digitalized on admission, had hyperthyroidism, mitral stenosis, auricular fibrillation, and congestive heart failure. Her venous pressure was 22 cm. of water, and her heart rate, 150, when she was given 8 c.c. of lanatoside C intravenously in divided doses. Within twenty-four hours the heart rate fell to 89, and, within forty-eight hours, the venous pressure was 9 cm. of water. After she recovered from her congestive failure, her basal metabolic rate was still +30 per cent. She refused to be operated on, but, with roentgen therapy and lanatoside C, has remained comfortable.

CASE 4.—A 58-year-old woman with a basal metabolic rate of +36 per cent had auricular fibrillation (ventricular rate 150) but no heart failure. She was given 8 c.c. of lanatoside C, and, on the next day, the electrocardiogram showed normal sinus rhythm, with a ventricular rate of 100. After she had taken Lugol's solution for twelve days her basal metabolic rate fell to +4 per cent, and she made an uneventful recovery after thyroidectomy.

CASE 5.—A 63-year-old woman with a basal metabolic rate of +32 per cent and auricular fibrillation (ventricular rate 126) responded promptly to the injection of lanatoside C with a slowing of her pulse rate to 70. The administration of Lugol's solution lowered her basal metabolic rate to +9 per cent, and she recovered quickly after her thyroidectomy.

A sixth patient who failed to respond to lanatoside C was admitted in a thyroid crisis, with a temperature of 107° F. and a grossly irregular heart (rate 150). She died on the third hospital day.

#### TOXICITY OF LANATOSIDE C

The comparative rarity of toxic reactions to lanatoside C has been striking. Not a single patient was unable to take lanatoside C, and only eight patients among the 256 who were given the drug were unable to tolerate the usual doses because of intractable nausea and vomiting. However, when the drug was withheld for two days and then given in doses of one tablet (0.25 mg.) per day, these symptoms failed to recur, and the usual beneficial effect was obtained. All had extrasystoles which disappeared in two days. In only three additional patients could extrasystoles be ascribed to lanatoside C, and two of these developed a bigeminal rhythm which disappeared within forty-eight hours. These latter two patients were unable to take digitalis purpurea, but they were relieved of their heart failure when smaller amounts of lanatoside C were given.

When symptoms of overdigitalization appear following the administration of lanatoside C, withdrawal of the medication for two days seems to remove all symptoms and signs of overdosage. In our experience, four to eight days elapse before these evidences of overdigitalization disappear when they are produced by digitalis purpurea. Complete heart block in the presence of auricular fibrillation occurred in the case of a woman with arteriosclerotic heart disease who had received five tablets (1.25 mg.) of lanatoside C daily for ten days. The block disappeared thirty-six hours after the administration of lanatoside C was discontinued and failed to recur when smaller doses were given.

In ten cases, nausea and occasional emesis occurred, but, despite these symptoms, the administration of the drug was continued in the same dosage (in most instances five tablets per day), and, to our surprise, both the nausea and vomiting disappeared. Transient nausea of this type has been noticed by Visseher<sup>20</sup> in dogs. We have never seen evidence of mental or visual disturbance as a result of giving lanatoside C.

Four patients who could not tolerate digitalis purpurea because of nausea, emesis, extrasystoles, and rhythmic bigeminy were able to take lanatoside C without distress and with great benefit. Four patients who alleged that they had never taken digitalis were given 8 c.c. of lanatoside C intravenously on admission, with only transient nausea, and, on the following day, we discovered that they had been fully digitalized on entry.

#### SUMMARY

1. Lanatoside C, which is a stable, crystalline glycoside derived from digitalis lanata, caused no anatomic changes in the heart muscle of the dog when it was given in therapeutic doses daily for a period of three months.

2. Lanatoside C, when administered intravenously to patients with auricular fibrillation, reduces the heart rate to normal within a period of two minutes to two hours. When administered orally, lanatoside C reduces the rate of the heart to normal within twenty-four to forty-eight hours.

3. Lanatoside C is efficacious in the treatment of congestive heart failure when normal sinus rhythm is present. In fact, the efficacy of lanatoside C in the presence of normal sinus rhythm is almost as great as when the heart failure is associated with auricular fibrillation.

4. Lanatoside C will often restore normal rhythm in cases of supra-ventricular paroxysmal tachycardia and auricular flutter. In eight of our 102 cases of nonparoxysmal auricular fibrillation, normal sinus rhythm became established spontaneously during treatment with lanatoside C.

5. Lanatoside C will reduce the pulse rate to normal in some cases of auricular fibrillation associated with hyperthyroidism, and, in at least one case, the venous pressure was brought down from 22 cm. of water to 9 cm. of water within forty-eight hours.

6. Lanatoside C seems definitely less toxic than preparations of digitalis purpurea. Some patients who cannot tolerate digitalis purpurea can take lanatoside C in sufficient doses to aid in the relief of their heart failure.

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# CALIBRATED PHONOCARDIOGRAPHY

## A NEW TECHNIQUE FOR CLINICAL USE

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STOCKHOLM

THE Argentines, Orías and Braun-Menéndez,<sup>1</sup> have recently published a monograph covering the most important methodologic and clinical results of phonocardiographic research. It is evident that, until the present time, most attention has been given to the four heart sounds. The third heart sound and the auricular sound, or the fourth heart sound as it is also called, have been subjected to intensive study. The different types of gallop rhythm have led to many investigations, with results of lasting theoretical and clinical value.<sup>1-3</sup>

Since 1906, when Einthoven constructed the first apparatus for phonocardiography, the method has been improved step by step. Nevertheless, it still has a number of unremedied technical defects; this is one of the reasons why it has not been more generally used clinically.

Other investigators have generally used an apparatus consisting of a microphone, amplifier, and oscillograph, and have recorded the electrocardiogram simultaneously. The frequency of the heart sounds varies from about 30 to a little over 1,000 cycles per second (Fig. 2). With the customary procedure, the whole of this frequency range is reproduced on a single curve. The disadvantages of using one curve are the following:

1. The sounds with a low frequency (the first heart sound, for example) have such great amplitude that the weaker murmurs of much higher pitch and smaller amplitude are drowned out.

2. No calibration has been used. Direct measurement, either of the frequency or the intensity of the heart sounds, has not been possible.

It is true that the frequency has been studied both by mathematical calculation and by the use of filters.<sup>4-7</sup> On the other hand, no objective measurements of the intensity have been made.

The intensity of murmurs has always been considered important in daily clinical practice. Levine,<sup>8</sup> for example, grades the systolic murmurs into "very slight," "slight," "moderate," "loud," "very loud," and "loudest possible." But, to quote Orías and Braun-Menéndez,<sup>1</sup> "we have to rely almost entirely on the results of auscultation. No objective studies have been made of the absolute intensity of murmurs."

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Consequently, there is need of a method which will register the intensity of all sounds produced by the heart.

I shall now describe a phonocardiograph which I have constructed in collaboration with Mr. Torkel Stordal, an electrical engineer.

### METHOD

The apparatus is made up of three main components:

1. A microphone of the crystal type.\*
2. A phonocardiograph (Fig. 1).
3. An electrocardiograph of the three-lead type† (Fig. 3).

The impulses are conducted from the microphone to the input of the phonocardiograph (*a*, in Fig. 1). Then they enter the first amplifier (*b*, in Fig. 1), where they are distributed into four channels, each of which contains an independent amplifier. On leaving the first amplifier, the impulses are led to a filter system (*c*, in Fig. 1).

*Filter System* (*c*, in Fig. 1).—Two types of filters are used, namely, high-pass filters which exclude the low frequencies but permit the passage of high ones, and low-pass filters which have the opposite effect. It is very important that the filters be highly selective, and this we have accomplished by means of special coils. With these filters, the whole of the frequency range covered by the heart sounds is divided into a series of separate frequency bands.

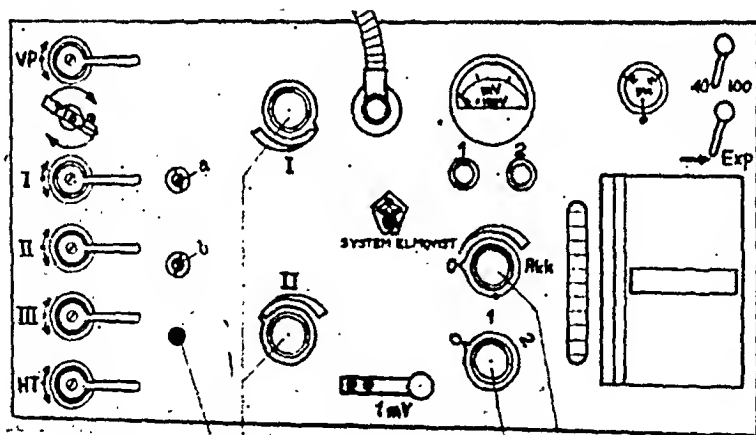


Fig. 3.—The manipulating board of the electrocardiograph.

Fig. 2 shows the distribution of the different frequency ranges in the musical scale. As will be seen, the band-pass filters are six in number. The first five overlap one another because it was found that otherwise the frequency ranges were so narrow that interference phenomena developed. As mentioned, the phonocardiograph has four independent channels, with built-in amplifying systems. By means of a switch, two of the channels are alternately connected with two different band-pass filters. From the filter units the impulses are led to the second amplifier (*d*, in Fig. 1) of the phonocardiograph, and thence to the moving-coil oscillograph. The moving coils, which are placed in the electrocardiograph, are manipulated by means of five handles (seen at the far left in Fig. 3).

\*Model 66, manufactured by Shure Brothers, Chicago, U. S. A.

†"Triplex," manufactured by the Instrument Laboratory of the University of Lund, Sweden.

The switching arrangement allows one to record (1) three electrocardiographic leads, together with two frequency ranges, or (2) only Lead II of the electrocardiogram and the four remaining frequency ranges. Thus, for every patient, two records are required, as follows:

PCG, Phonocardiogram; ECG, Electrocardiogram.

A. { PCG below 100 cycles/sec.  
ECG Lead I.  
ECG Lead II.  
ECG Lead III.  
PCG 500 to 1000 cycles/sec.

B. { PCG 50 to 175 cycles/sec.  
PCG 100 to 250 cycles/sec.  
ECG Lead II.  
PCG 175 to 400 cycles/sec.  
PCG 250 to 500 cycles/sec.

*Calibration of Intensity.*—In addition to the amplification and filter apparatus just described, an apparatus for calibration of the amplitude of the sounds is also built into the phonocardiograph. It consists of tube oscillators which deliver tones of a known pitch and amplitude. These oscillators are placed far to the left in the second amplifier (*d*, in Fig. 1). The tones emitted have frequencies of 70, 175, 275, 375, and 700 cycles per second. The tone 70 lies both within the band below 100 cycles and in the 50- to 175-cycle band. The other tones fall into the middle of their frequency ranges. By means of voltage dividers (consisting of a tapped resistance), it is possible to reduce the full voltage sent out in the tube

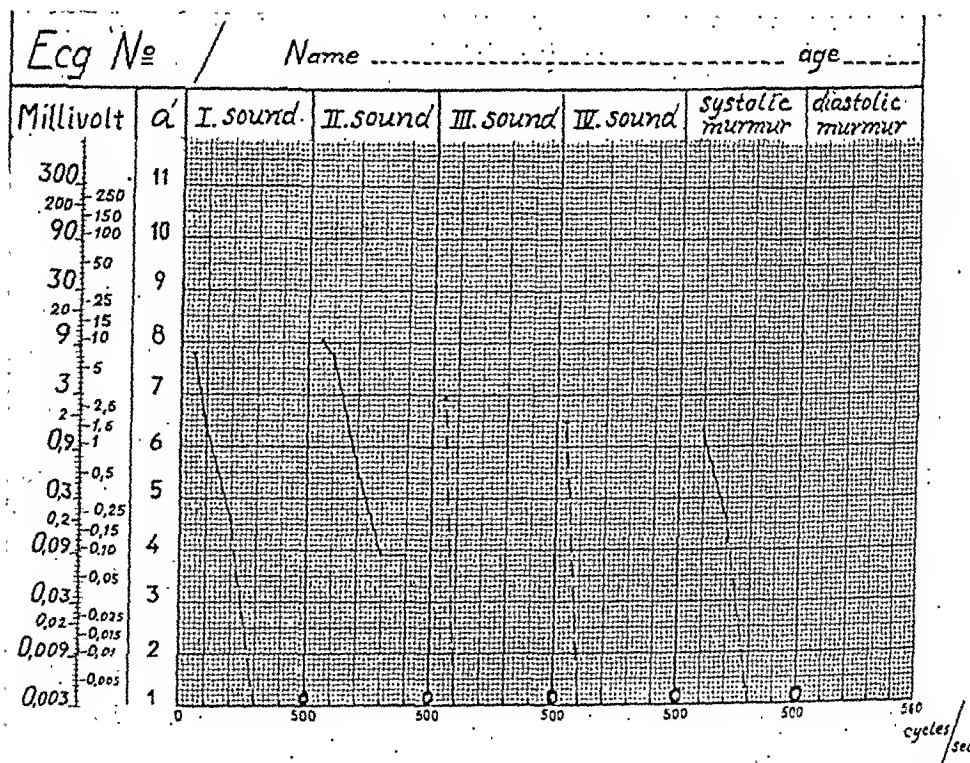


Fig. 4.—Diagram of calibrated phonocardiography (Case 2, Fig. 6). Abscissa: the different frequency ranges in cycles per second. Ordinate: the amplitudes (voltages) of the sounds. Logarithmic scale in millivolts from the microphone. Under  $\alpha$  are given the voltage divider positions (see text and *e* in Fig. 1).

oscillators. Thus, in every case, the voltage of the impulses coming in from the microphone can be compared with the calibration voltage. The latter is measured in millivolts, within the limits of 0.003 to 300 millivolts. The absolute number of millivolts, accordingly, is dependent upon the microphone, and, therefore, every apparatus must be adjusted, unless it is possible to obtain microphones with exactly the same physical characteristics.

*Graphic Registration.*—The results are recorded in a coordinate system, as is seen in Fig. 4. The first, second, third, and fourth heart sounds, and the systolic and diastolic murmurs are placed in sequence along the abscissae of the phonocardiogram, each one in a separate part. The different frequency ranges are measured in cycles per second. The intensity of the different sounds, in millivolts, according to a logarithmic scale, is recorded along the ordinates. With printed charts of this kind, it takes little time to draw the curves. Fig. 4 is the graph obtained in Case 2 (see later). The following general facts emerge from

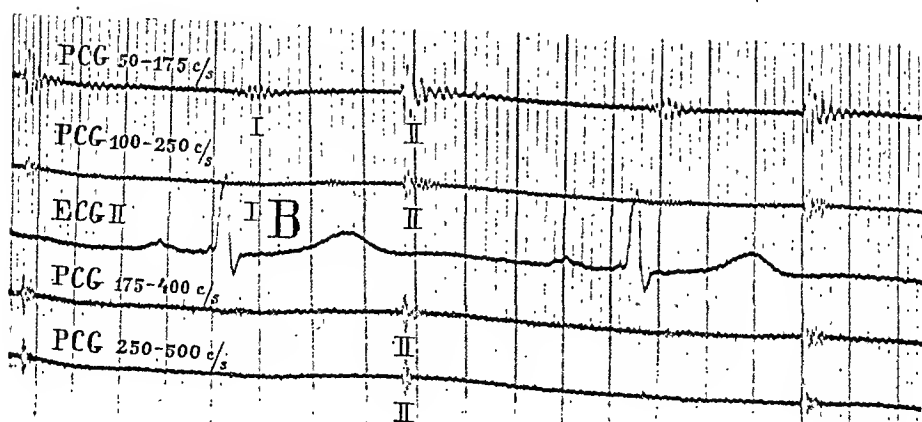
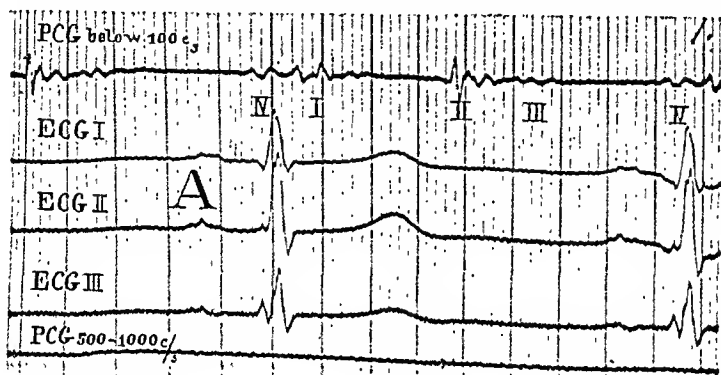


Fig. 5.—Case 1. A is first record, and B, second record (see p. 157). PCG, Phonocardiogram; ECG, electrocardiogram; I, first heart sound; II, second heart sound; III, third heart sound; IV, auricular, or fourth, heart sound; S.M., systolic murmur; P.D.M., protodiastolic murmur; P.M., presystolic murmur; C.M., continuous

consideration of the different curves in this figure: The greatest amplitude of the first and second heart sounds is below 100 cycles per second, and this amplitude decreases rapidly with increasing frequency. The first sound, especially, has relatively few overtones, whereas the overtones of the second sound continue up to 500 cycles per second. The third and fourth heart sounds are registered only in the frequency range below 100 cycles. The accidental systolic murmur is registered in the 50- to 175-cycle range, where it has an amplitude of about 1.5 millivolts, and in the 100- to 250-cycle range, where it has an amplitude of 0.18 millivolt. The curves also illustrate the well-known fact that the ear is relatively much less sensitive to low than to high tones. The third and fourth sounds, which have low frequencies and no overtones, have a much greater amplitude than the slight systolic murmur. Yet the ear cannot perceive these sounds, although the much weaker accidental murmur of higher pitch can be

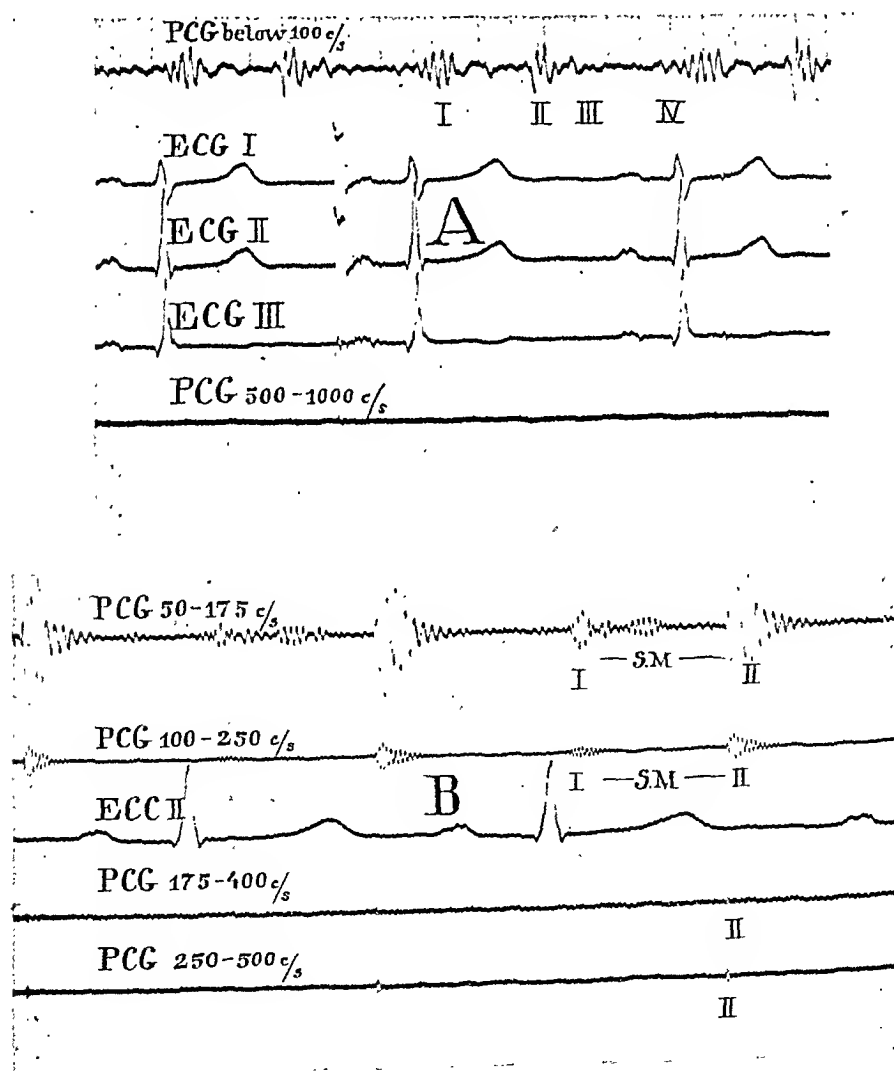


Fig. 6.—Case 2. For explanation of signs see Fig. 5.

heard without difficulty. Furthermore, the diagram shows the great differences in degree of amplification in the different frequency ranges. In the 250- to 500-cycle frequency range, the amplification in this case was about one hundred times as great as in the range below 100 cycles per second. This is particularly evident from the graph of the second heart sound.

#### CASE REPORTS

CASE 1 (Fig. 5), *Normal*.—The patient was a boy, 7 years old, with no signs of cardiac disease.

Physical examination revealed pure heart sounds.

The electrocardiogram was normal.

Phonocardiogram.—All of the four heart sounds were registered, the first up to 250 cycles per second, and the second, with its overtones, up to 500 cycles per second. There were no murmurs.

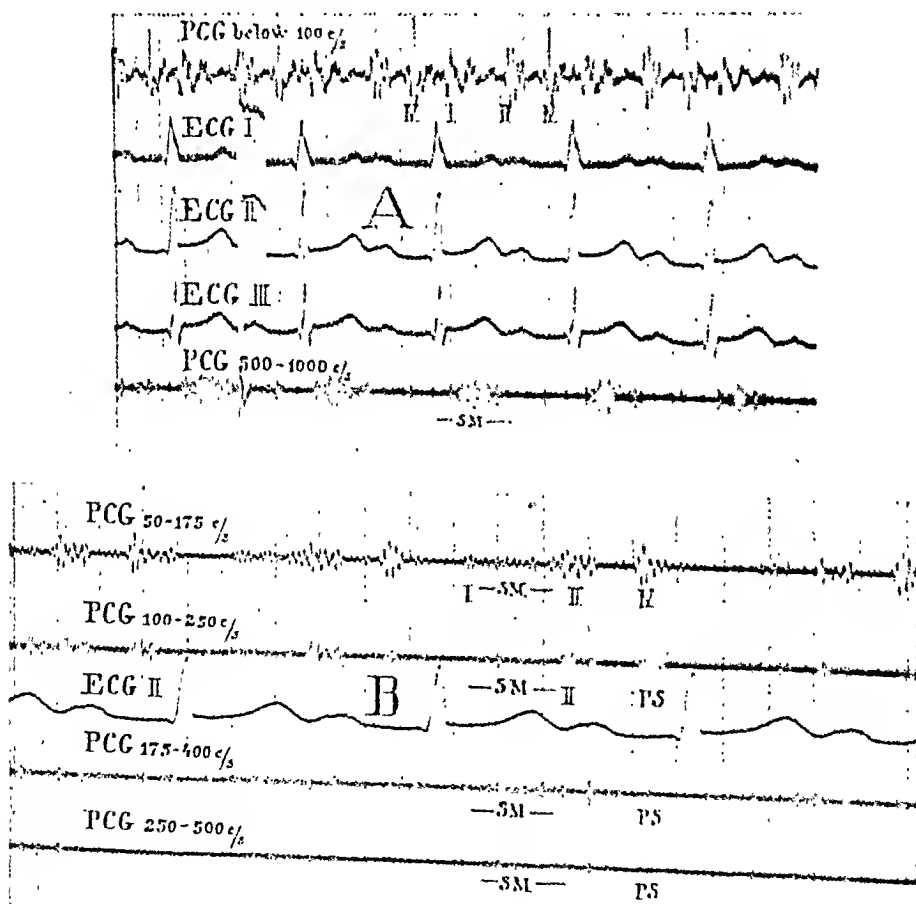


Fig. 7.—Case 3. ECG and PCG taken May 17, 1933. For explanation of signs see FIG. 5.

CASE 2 (Figs. 4 and 6), *Probably Accidental Systolic Murmur*.—The patient was a healthy 10-year-old girl who had been previously unaware of any heart defect.

Physical examination revealed a faint systolic murmur, maximal over the apex and slightly fainter in the sitting position.

The electrocardiogram showed a P-Q interval of 0.17 sec., a normal QRS complex, with no axis deviation, a weakly diphasic T<sub>2</sub>, and normal S-T segments.

Phonocardiogram.—All four heart sounds were registered. A faint systolic murmur (S.M.) was registered in the 50- to 175- and 100- to 250-cycle ranges. For the graphic registration, see under Graphic Registration and Fig. 4.

CASE 3 (Figs. 7 and 8), *Rheumatic Pancarditis, With Mitral Defect*.—A girl, R. J., aged 11 years, had a typical history of joint manifestations and high fever of long duration. Pallor and slight dyspnea were present.

Physical examination (May 17, 1939) showed great enlargement of the heart. The left border was located at the anterior axillary line, and the right, 2 cm. beyond the right sternal border. Agitated heart action and palpitation were observed, and there was a distinct gallop rhythm over the apex which lifted the stethoscope in time with it. There was a hissing, musical systolic murmur over the apex, as well as a short presystolic murmur.

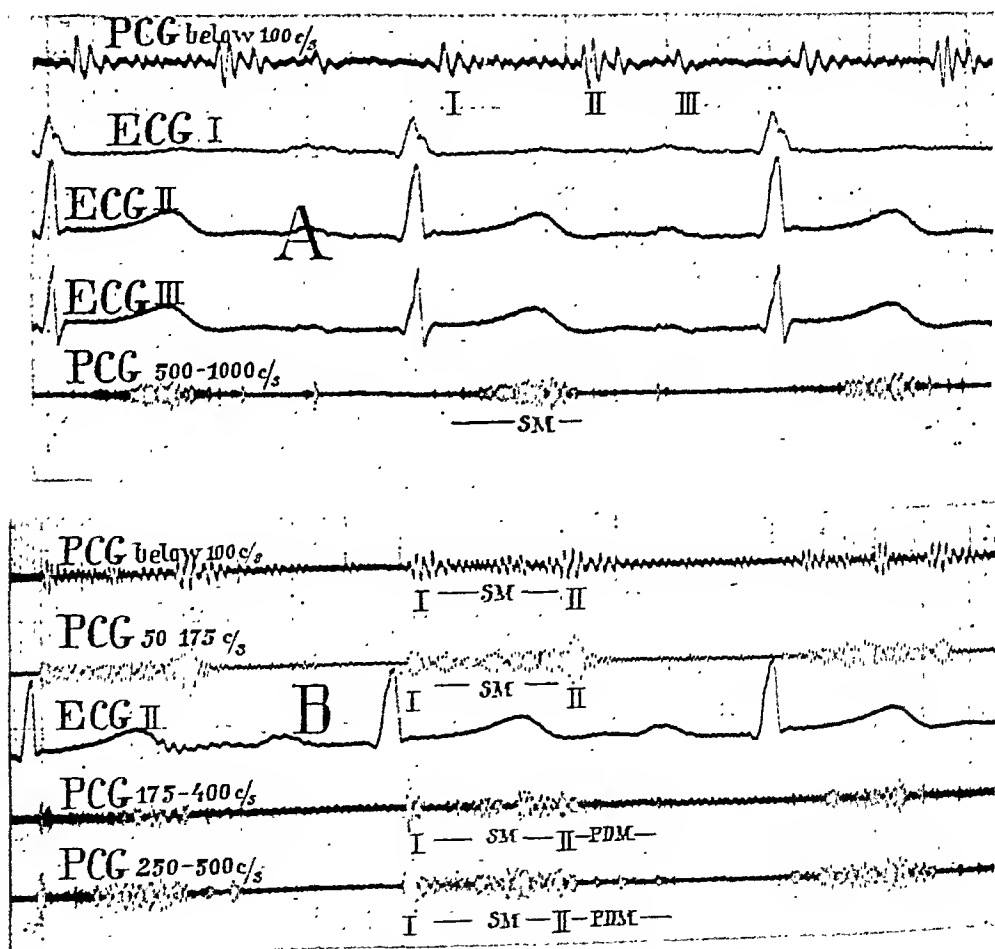


Fig. 8.—Case 3. ECG and PCG taken Feb. 6, 1940. For explanation of signs see Fig. 5.

Roentgenologic examination showed a greatly enlarged heart, with a mitral configuration.

The electrocardiogram showed normal sinus rhythm, a rate of 110 beats per minute, partial A-V block, with prolongation of the P-Q interval to 0.26 sec., distinctly elevated S-T segments in Leads II and III, and broad P waves, lasting 0.11 sec.

Phonocardiogram.—Under 100 cycles per second, an extremely powerful auricular sound, with a greater amplitude than the first and second heart sounds, was registered. The overtones of the fourth sound could be followed up to 500 cycles per second and corresponded to the presystolic murmur (P.S.). There was a systolic murmur of high frequency which had its greatest amplitude between 500 and 1,000 cycles per second (S.M.).

Examination on Feb. 6, 1940, showed improvement in the general condition and fairly good compensation. The patient was out of bed several hours every day, but the slightest exertion made her short of breath and tired.

Physical examination showed that the right and left borders of the heart were located 3 cm. beyond the left mammary line and 2 cm. beyond the right sternal border, respectively. Palpitation was still present. The presystolic murmur had disappeared, but there was still a long, hissing, musical systolic murmur of maximal intensity over the apex.

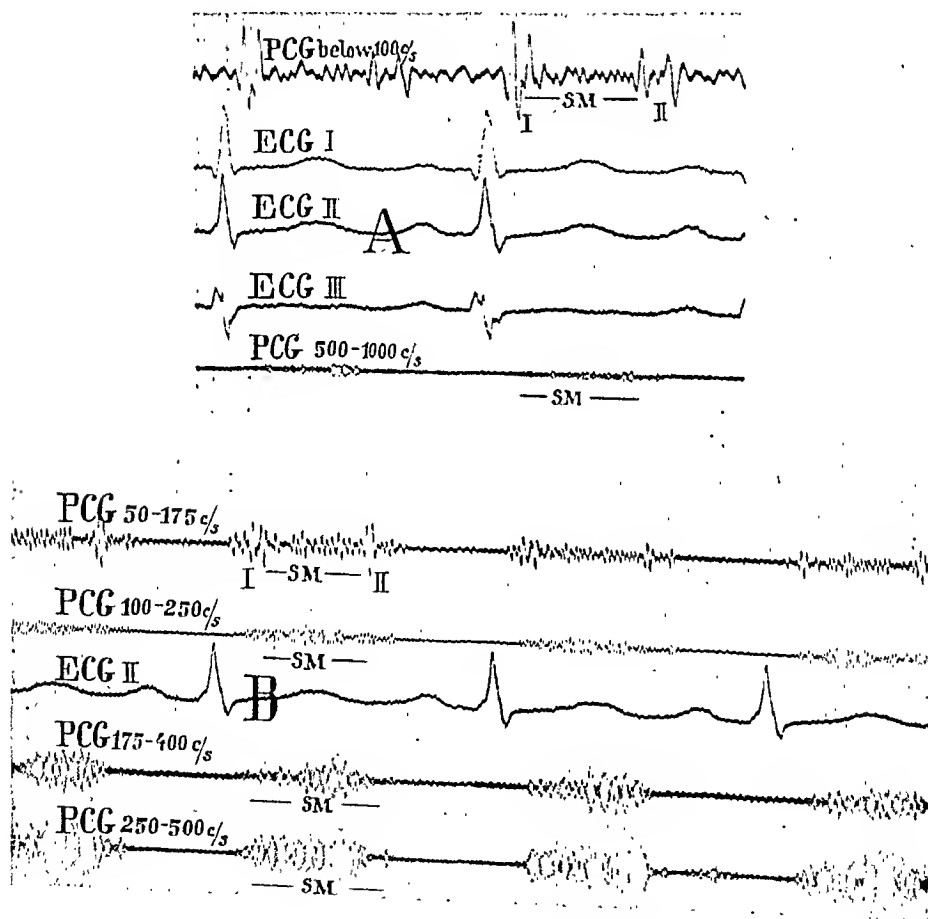


Fig. 9.—Case 4. For explanation of signs see Fig. 5.

Electrocardiographic examination showed that the heart rate had slowed to about 95 beats per minute. The electrical axis lay somewhat farther to the right. The P-Q interval of 0.25 sec. showed that partial block was still present. The P waves were broader, measuring 0.12 sec. There was still an elevation of the S-T segments in Leads II and III.

Phonocardiogram.—The powerful auricular sound had disappeared, as had the presystolic murmur. The third sound was distinct. A powerful systolic murmur of 50 to 1,000 cycles per second was registered.



**Epiclerisis:** This case was that of an eleven-year-old girl with rheumatic pancarditis and mitral stenosis. Electrocardiograms showed partial A-V block, changes in the S-T segments, and broad P waves. On the first examination, phonocardiograms showed an auricular gallop and a presystolic murmur. These phenomena disappeared when the patient grew better, but a drawn-out, musical systolic murmur remained.

**CASE 4 (Fig. 9), Congenital Heart Defect.**—The patient, G. S., was a girl, aged 2 years and 1 month. The defect was detected when she was 6 months old. There were no signs of cardiac insufficiency. At birth she weighed 3,545 Gm., and, on admission, 12.4 kg. Her general condition was good, and she showed no cyanosis.

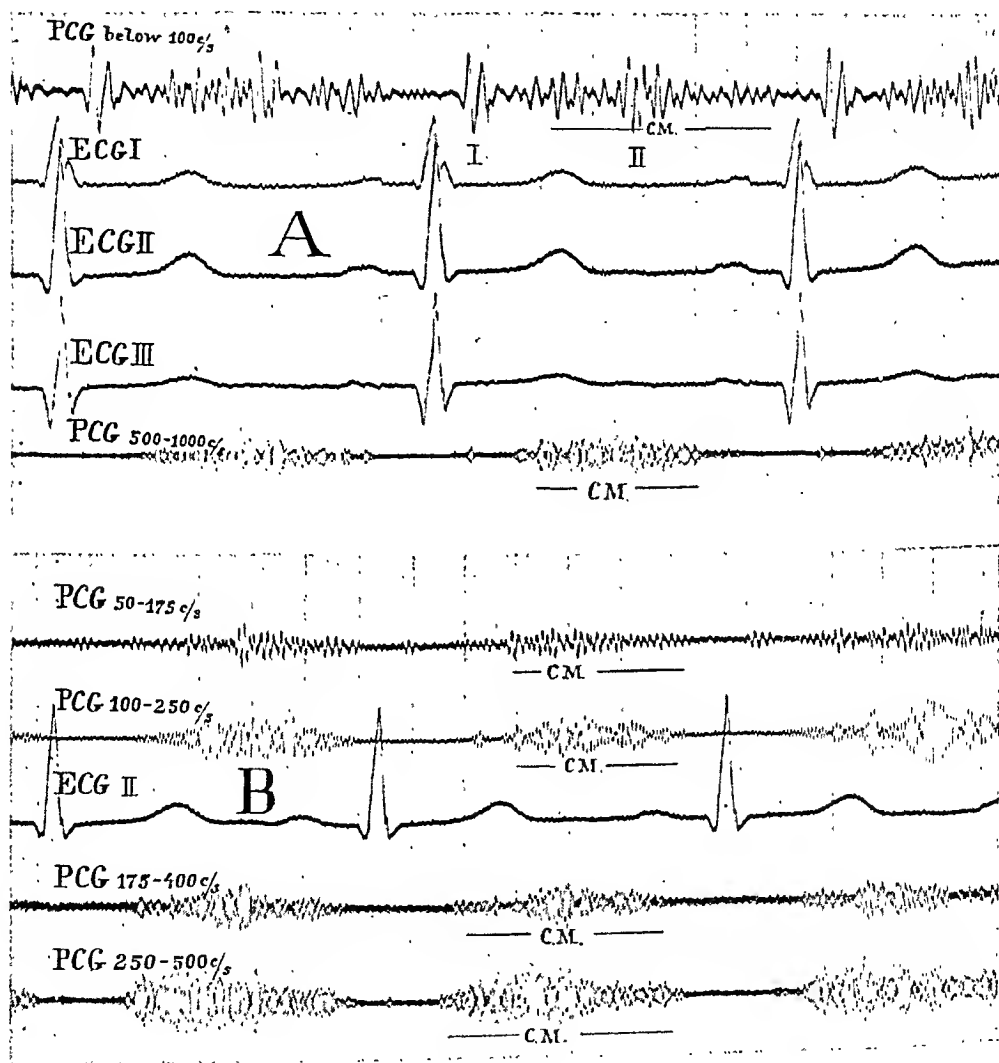


Fig. 10.—Case 5. For explanation of signs see Fig. 5.

Physical examination disclosed no enlargement of the heart, but a loud, long systolic murmur was heard over the whole cardiac region; it was of maximal intensity in the second intercostal space to the left of the sternum.

Roentgenographic examination showed slight enlargement of the heart to the left.

The electrocardiogram showed an insignificant sinus arrhythmia, a rate of 100 to 110 beats per minute, a large  $S_{II}$ , left axis deviation (+10 degrees), and a P-Q interval of 0.15 sec. The T waves were positive in all leads.

Phonocardiogram.—The second sound was split. There was a powerful systolic murmur between 50 and 1,000 cycles per second.

CASE 5 (Fig. 10), *Congenital Heart Defect* (probably patent ductus arteriosus).—R. T., a girl, aged 6 years and 3 months, had a congenital defect which was discovered when she was 4 months old. She was pale and thin. No cyanosis or symptoms of cardiac insufficiency were observed.

Physical examination revealed a loud systolic thrill. The right and left borders of the heart were located 2 cm. beyond the left mammary line and 2 cm. beyond the right sternal border, respectively. There was a harsh, loud, rumbling, continuous murmur which was partly systolic and partly diastolic; it was of maximal intensity over the second intercostal space to the left of the sternum.

Roentgenographic examination showed that the heart was enlarged to the left and posteriorly.

The electrocardiogram exhibited sinus rhythm, with a rate of about 90 beats per minute. The voltage of the QRS complex was slightly high, but the complex was otherwise normal, with no axis deviation. The P-Q interval was 0.14 sec. The T waves and S-T segments were normal.

Phonocardiogram.—The frequency of the heart sounds was below 100 cycles per second. The record was dominated by the unusually loud, long, continuous murmur which lasted from the middle of systole to the end of diastole; it had a large amplitude and a frequency of 50 to 1,000 cycles per second.

The fact that the murmur was continuous suggested the possibility of patency of the ductus arteriosus.

#### SUMMARY

A new phonocardiographic technique is described; it has the following advantages over the previous methods:

1. The whole frequency range covered by the heart sounds is divided by filters into six frequency ranges. These six ranges are registered simultaneously. Each range can be amplified independently and to different degrees, if desired. Thus the heart sounds, with their relatively low frequency and large amplitude, are amplified only slightly in comparison to their overtones and any murmurs which may be present. The low-frequency ranges, particularly the range below 100 cycles per second, are reserved for the heart sounds, while the higher ranges reproduce the overtones of the heart sounds and any murmurs which may be present.

2. In order to register weaker murmurs accurately, disturbances from both inside and outside the apparatus are eliminated as much as possible by means of the filters.

3. By simultaneous calibration of the amplitude of the sound waves, that is, measuring the degree of amplification in each separate frequency range, data are also obtained on the intensity of the sounds.

4. Calibrated phonocardiography, which has so far been used only on children, gives promise of being a valuable diagnostic aid in practical clinical work, especially in differentiating between the murmurs associated with organic heart defects and those of a "functional" nature. Because the method permits exact measurement of all heart

sound phenomena, it should be used to complement auscultation, in order to minimize the personal factor in this important part of the physical examination.

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# HEMOPTYSIS IN RHEUMATIC HEART DISEASE

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HEMOPTYSIS has long been recognized as a complication of rheumatic heart disease. The discussion of the subject in medical journals and standard textbooks of cardiology, however, gives little indication of its great incidence or importance.<sup>1-11</sup> In spite of its frequency and, in some cases, rapidly fatal consequences, the mechanism which produces the hemorrhage is often obscure, and treatment in severe cases is unsatisfactory or nonexistent. It seemed desirable, therefore, to investigate certain aspects of this complication of rheumatic heart disease, and the present paper deals with a preliminary study of the subject.

Five hundred twenty-one patients with rheumatic heart disease were admitted to the Beth Israel Hospital between 1928 and 1937, inclusive, and, of these, fifty had hemoptysis\* prior to admission or during their hospital stay, which is an incidence of 9.5 per cent. The symptoms which were associated with the hemoptysis varied a great deal; some patients had none, but others complained of pain in the chest, palpitation, dyspnea, cyanosis, wheezing, acute pulmonary edema, weakness, faintness, and collapse. The most common symptoms were palpitation, pain in the chest, and dyspnea. Some patients showed cyanosis and acute pulmonary edema.

The average age at the onset of hemoptysis was 33.4 years; the youngest patient was 14, and the oldest, 54 years old.

## I. ANATOMIC, PATHOLOGIC, AND PHYSIOLOGIC ABNORMALITIES ASSOCIATED WITH HEMOPTYSIS

As stated above, the mechanism which produces hemorrhage in cases of rheumatic heart disease is often obscure. Predisposing factors were conspicuously absent; an acute upper respiratory infection preceded the hemoptysis in three cases, and in two others the hemorrhage occurred during pregnancy. In one case the hemoptysis always followed severe exertion. There was no evidence that any of our patients had a hemorrhagic diathesis. The rheumatic infection was active in twelve of the fifty cases, but in many instances this diagnosis was not made until post-mortem examination disclosed acute valvular changes. Six patients had cerebral, renal, or axial embolism, but not necessarily at the time of hemoptysis, and in not all of these cases was pulmonary infarction the cause of the hemorrhage. Thrombi were found in the left auricle in

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\*Only patients who had frank hemorrhage were selected; those whose sputum was merely bloodstreaked were excluded.

one case, and in the right auricle in three others. Sclerosis of the pulmonary vascular tree was mentioned in the pathology protocols in six cases, which is an incidence of 36 per cent of the autopsy cases. Since this pathologic process was not investigated specifically, it is probable that many more patients had lesser degrees of pulmonary vascular sclerosis, and that 36 per cent represents the incidence of advanced and easily recognizable vascular disease.

Two patients had subacute bacterial endocarditis; one had a lung abscess; and two had bronchiectasis.

*Abnormalities in the Cardiac Mechanism.*—Twenty of the fifty patients had chronic auricular fibrillation; three had paroxysmal auricular fibrillation; and one had paroxysmal auricular flutter. The only case in the entire series in which there was a clear relationship between disordered mechanism of the heartbeat and hemoptysis was one in which the hemorrhage occurred during an attack of paroxysmal auricular tachycardia. The possibility of this relationship, however, cannot be excluded in the other cases of paroxysmal arrhythmia.

*Heart Size and Valve Involvement.*—All patients with hemoptysis had mitral stenosis\* except one, and he had aortic insufficiency. In this case the hemorrhage was caused by a lung abscess. Twenty-seven of the patients had mitral stenosis as the only valve lesion, while the remaining twenty-two had, in addition, aortic, and, in three cases, tricuspid valve disease.

Nineteen, or 38 per cent, of the entire group had markedly enlarged hearts; sixteen had slight to moderate cardiac enlargement; and in nine cases there was no demonstrable enlargement of the heart. The size of the heart was unknown in four cases; two patients with subacute bacterial endocarditis were not included in this classification. The size of the heart was ascertained at autopsy in sixteen cases, and, in many of the remaining ones, by teleroentgenograms.

*Congestive Failure and Pulmonary Infarction.*—Only eight of the fifty patients had recognizable congestive failure† prior to, or at the time of, the initial hemoptysis, whereas pulmonary infarction was present in twenty-three cases, in thirteen of which there was autopsy confirmation. Of the total number of eight patients with congestive failure at the time of the initial hemoptysis, seven had pulmonary infarction. Seven additional patients whose hemoptysis was associated with pulmonary infarction developed congestive failure at varying intervals after the hemoptysis.

## II. MECHANISM OF HEMOPTYSIS

In attempting to arrive at some understanding of the mechanism underlying hemoptysis in rheumatic heart disease, three facts stand

\*The diagnosis of mitral stenosis was questionable in two cases.

†I.e., abnormally high venous pressure, enlargement of the liver, edema, and accumulation of fluid in serous cavities.

out above all others; mitral stenosis was present in every case (except one, in which the hemorrhage was caused by a lung abscess), pulmonary infarction was diagnosed in twenty-three cases, and, prior to the onset of hemoptysis, congestive failure was present in only eight cases.

In twenty-three, or almost half of the series, the hemorrhage was accounted for by pulmonary infarction, which is a recognized cause of hemoptysis. Pulmonary infarction may result from embolism (the source may be right auricular thrombi or peripheral venous thrombosis), or from pulmonary thrombosis, which is favored by pulmonary arteriosclerosis, congestive failure, or both. It is noteworthy that pulmonary infarction was found in seven of the eight cases of congestive failure and in only two of the nine cases in which the size of the heart was normal. Following the initial hemoptysis in the latter two cases, the size of the heart increased progressively over a period of many months, and, at post-mortem examination in one of them, marked pulmonary arteriosclerosis and multiple thrombosis were found. Therefore, pulmonary infarction is the most likely cause of hemoptysis in the presence of congestive failure, but may be excluded if the patient has no cardiac enlargement. If, however, pulmonary infarction occurs when the patient has no cardiac enlargement, and particularly if hemoptysis is followed by a progressive increase in the size of the heart, a severe degree of pulmonary arteriosclerosis may be the underlying cause.

In most of the remaining cases the hemoptysis was caused, undoubtedly, by mitral stenosis alone, without gross evidence of congestive failure, i.e., by a forceful right ventricle, mitral obstruction, pulmonary hypertension, and arteriosclerosis. McGinn and White<sup>12</sup> have explained the occurrence of acute pulmonary congestion and cardiac asthma in cases of mitral stenosis by stating that when the heart is speeded up by effort, excitement, or paroxysmal tachycardia, the strong, enlarged right ventricle expels more blood into the pulmonary circulation than can be passed through the stenosed mitral valve in the same unit of time. Stewart,<sup>10</sup> in discussing hemoptysis in three cases of mitral stenosis, came to the same conclusions regarding its mechanism. It is likely that the occurrence of hemorrhage depends not only on the degree of congestion and the height of the pulmonary pressure, but also on the presence of sclerosed vessels which rupture under the strain of congestion and hypertension (pulmonary). Proff<sup>13</sup> and Oppenheimer and Schwartz<sup>11</sup> have discussed the possibility that diapedesis may be a cause of pulmonary hemorrhage, but this view is not justified by the available facts.

Finally, hemorrhage may be caused by active rheumatic infection. Brenner<sup>8</sup> states that rheumatic infection of the pulmonary arteries is common, and that involvement of capillaries and venules may be the cause of hemoptysis early in the disease. There was evidence of active rheumatism in twelve of our cases. In two of the three cases in which

death occurred within one or two days, the diagnosis was made clinically, and, at post-mortem examination, in all three. The possibility of rheumatic infection of the pulmonary vessels, however, was not investigated.

It is, of course, necessary, when hemoptysis occurs in a case of rheumatic heart disease, to exclude intercurrent pulmonary disease as its source. All the known causes of hemoptysis must be considered. In the present series, one patient had a lung abscess, and two others had bronchiectasis.

If intercurrent pulmonary disease can be ruled out, and the patient is comparatively young, and especially if "left ventricular failure" can be excluded, it may be assumed that mitral stenosis is present. Hemoptysis in such cases may be of help in distinguishing between an Austin-Flint murmur and the murmur of aortic regurgitation, or in the diagnosis of mitral stenosis.

### III. PROGNOSIS

At the time this study was completed, thirty-three, or 66 per cent, of the patients were dead; the average duration of life following the initial hemoptysis was 32.5 months. None of the common complications of rheumatic heart disease, with the exception of subacute bacterial endocarditis, has such a serious prognostic implication. Three patients died within one or two days after the onset of hemorrhage. Such sudden death from hemoptysis in young cardiacs (rheumatic) is a very dramatic, unexpected, and unpredictable event; as in these cases, the patients may have but minimal cardiac enlargement and be unburdened by failure or abnormal rhythm. Eight patients died within one month; seventeen, within a year; and twenty-one, or 42 per cent, within two years; only five patients survived their initial hemoptysis five years or longer. In the cases of fatal hemoptysis, therefore, only 15 per cent of the patients survived five years or longer, and, of the remaining cases, the average duration of life after the initial hemoptysis was less than a month in 28 per cent, a year, or less, in 60 per cent, and two years, or less, in 75 per cent.

The average length of time from the initial hemoptysis to the last follow-up examination of the seventeen patients who are still living was thirty-nine months, and, to date, only five of these have survived five years or longer.

Grant<sup>14</sup> has analyzed the after histories for ten years of 1,000 men suffering from heart disease. There were 433 patients with mitral stenosis, either alone or in combination with aortic regurgitation, and, of these, 166, or 38 per cent, had died in ten years, and twenty-five, or 5.9 per cent, had had hemoptysis. This contrasts, in the present series, with a mortality of 66 per cent, and an incidence of hemoptysis of 10

per cent. Grant showed, however, that the mortality among patients with greatly enlarged hearts and congestive failure was much higher than in the series as a whole; indeed, his main thesis was to demonstrate that congestive failure and marked cardiac enlargement are the two most important and serious prognostic indications. Nevertheless, it is noteworthy that, of 197 patients with uncomplicated mitral stenosis, those with the greatest degree of cardiac enlargement and congestive failure

TABLE I

DISTRIBUTION OF VARIOUS FACTORS IN PATIENTS WHO SURVIVED TWO YEARS OR LESS, AND IN THOSE WHO SURVIVED MORE THAN TWO YEARS

	20 PATIENTS WHO DIED WITHIN 2 YEARS	19 PATIENTS WHO SURVIVED MORE THAN 2 YEARS
*Heart size 0-++	9	†9
Heart size +++	11	7
Congestive failure	6	1
Over 30 years of age	10	12
Pulmonary infarcts	13	6
Hemorrhage (large)	6	7
Hemorrhage (small)	5	5
Auricular fibrillation (chronic)	9	11
Multiple valve involvement	14	5

\*In all the tables 0 indicates no cardiac enlargement;

+, slight cardiac enlargement;

++, moderate cardiac enlargement;

+++, marked cardiac enlargement; and

++++, greatest cardiac enlargement.

†Nothing known about size of the hearts of three patients who survived more than two years.

TABLE II

MORTALITY AND LONGEVITY, AS RELATED TO PULMONARY INFARCTION

PULMONARY INFARCTION				NO PULMONARY INFARCTION			
23 CASES	1 YEAR	2 YEARS	MORE THAN 2 YEARS	27 CASES	1 YEAR	2 YEARS	MORE THAN 2 YEARS
18 died	13	2	3	15 died	6	1	8
5 living	1	1	3	12 living	4	2	6

TABLE III

MORTALITY AND LONGEVITY IN CASES OF MITRAL STENOSIS (NUMBER OF CASES OF PULMONARY INFARCTION IS INDICATED)

27 CASES	1 YEAR	2 YEARS	MORE THAN 2 YEARS	INFARCTION	NO INFARCTION
14 died	6	1	7	7	7
13 living	4	2	7	3	10

survived four to five years. In our series, the average length of life of the patients with mitral stenosis alone was fifty months, but only four of the twenty-seven had great enlargement of the heart. The mortality in Grant's forty-three cases of aortic stenosis and regurgitation was 65 per cent, whereas, in the present series, thirteen of the fifteen patients with this valve lesion died, a mortality of 86 per cent, and eight had marked cardiac enlargement.



TABLE IV

MORTALITY AND LONGEVITY IN CASES OF MULTIPLE VALVE INVOLVEMENT  
(NUMBER OF CASES OF PULMONARY INFARCTION IS INDICATED)

22 CASES	1 YEAR	2 YEARS	MORE THAN 2 YEARS	INFARCTION	NO INFARCTION
18 died	13	2	3	11	7
4 living	1	1	2	2	2

TABLE V

MORTALITY AND LONGEVITY IN RELATION TO SIZE OF THE HEART (KNOWN IN 44 CASES;  
ONE CASE OF SUBACUTE BACTERIAL ENDOCARDITIS EXCLUDED), SHOWING THE  
DISTRIBUTION OF SINGLE OR MULTIPLE VALVE INVOLVEMENT  
AND PULMONARY INFARCTION

		1 YEAR	2 YEARS	3 YEARS	4 YEARS	5 YEARS OR MORE	
No enlargement							
9	died 1					1 ac	a 1 b 0 c 1
	living 8	2 a	1 a	2 a	1 ac	2 {1a 1b	a 7 b 1 c 1
Slight enlarge- ment							
6	died 5	4 {2 ac 1 be 1 b	0	0	0	1 be	a 2 b 3 c 4
	living 1	1 a					a 1 b 0 c 0
Moderate en- largement							
10	died 6	5 {1 a 2 b 2 ac	0	0	1 be	0	a 2 b 3 c 3
	living 4	1 a	2 {1 a 1 be	1 a	0	0	a 3 b 1 c 1
Marked enlarge- ment							
14	died 11	7 {1 b 6 be	1 ac	1 a	0	2 a	a 4 b 7 c 7
	living 3	1 be	0	0	0	2 {1 ac 1 b	a 1 b 2 c 2
Greatest enlarge- ment							
5	died 4	1 be	2 {1 b 1 be	1 b	0	0	a 0 b 2 c 2
	living 1	0	0	0	0	1 ac	a 1 b 0 c 1

a, Single valve involvement; b, multiple valve involvement; c, pulmonary infarction.

TABLE VI

DATA IN TWELVE CASES IN WHICH DEATH OCCURRED WITHIN SIX MONTHS FOLLOWING THE ONSET OF HEMOPTYSIS

AGE (YEARS)	HEART SIZE	MITRAL STENOSIS ALONE	MITRAL STENOSIS AND AORTIC DISEASE	PUL- MONARY IN- FARCTION	CON- GESTIVE FAILURE	SIZE OF HEMOR- RHAGE	LENGTH OF SURVIVAL AFTER FIRST HEM- ORRHAGE
14	++	*		*	0	unknown	2 days
21	+	*		*	0	unknown	1 day
40	++	*		0	0	copious	6 months
51	+++		*	0	0	unknown	few weeks
43	+++		*	*	0	unknown	2 weeks
43	+		*	*	0	copious	2 days
25	+++		*	0	0	unknown	6 months
21	++++		*	*	unknown	small	3 weeks
44	++		*	0	*	unknown	1 month
34	+++		*	*	0	unknown	2 months
36	++		*	0	0	small	4 weeks
42	+++		*	*	*	unknown	2 months

A complete analysis of our cases is shown in Tables I to VI, indicating the effect of various factors on prognosis. Other factors which might have influenced prognosis were negligible. There were four patients with hypertension; three of these were alive six, seven, and nine years, respectively, after the onset of hemoptysis, but the fourth died in a few weeks. A diagnosis of paroxysmal dyspnea was made in one case, and asthmatic bronchitis in another; both of these patients are still living. Acute pulmonary edema was diagnosed in two cases, and both patients are dead. Cardiac asthma was not mentioned in any case, although wheezing occurred in eight. Of these patients, four died one month, and one, two, and three years, and four are still alive one month, a few months, four years, and nine years, respectively, following the onset of hemoptysis.

It may be concluded that in cases of rheumatic heart disease in which there is no cardiac enlargement, hemoptysis, as a rule, appears to be of little or no prognostic significance. Most of these patients have a single valve lesion, namely, mitral stenosis. Half of our patients with slight cardiac enlargement died within one or two days after the onset of hemoptysis, and two-thirds died within a year. Since these deaths occurred in cases in which the prognosis was usually excellent, it is obvious that in such cases hemoptysis must be regarded as a grave prognostic indication. Among the remaining patients the mortality was higher, and the length of survival shorter, than would have been predicted on the basis of degree of cardiac enlargement and congestive failure alone. Hemoptysis, therefore, enhances the seriousness of the prognosis in this group. The mortality was higher among the patients with pulmonary infarction than in the series as a whole. The evidence indicates that hemoptysis during pregnancy is not necessarily in-

dicative of a bad prognosis, for the two pregnant women in our series were among the longest survivors.

#### SUMMARY

1. Fifty cases of rheumatic heart disease in which hemoptysis occurred are analyzed. This complication is encountered in at least 10 per cent of all adults with rheumatic heart disease who are admitted to a general hospital. In our series, the average age at the onset of hemoptysis was 33.4 years.

2. The symptoms most commonly associated with hemoptysis were palpitation, pain in the chest, and dyspnea.

3. The associated anatomic, pathologic, and physiologic abnormalities, in the order of their frequency, were:

- (a) Mitral stenosis, in all but one case.
- (b) Pulmonary infarction, in twenty-three cases.
- (c) Multiple valve involvement, in twenty-two cases.
- (d) Chronic auricular fibrillation, in twenty cases.
- Paroxysmal arrhythmia, in five cases.
- (e) Marked cardiac enlargement, in nineteen cases.
- (f) Active rheumatic infection, in twelve cases.
- (g) Congestive failure, in eight cases.
- (h) At autopsy:

    Easily recognizable pulmonary vascular sclerosis in six cases.

    Right auricular thrombi in three cases.

4. The prognosis and the mechanism of hemoptysis are discussed.

5. It is noteworthy that only eight patients had congestive failure prior to, or at the time of, the initial hemoptysis, and that nine had hearts of normal size. Pulmonary infarction is the most likely cause when there is congestive failure and may be excluded when the heart is of normal size. The combination of pulmonary infarction, a heart of normal size, and progressive cardiac enlargement following hemoptysis may indicate a severe grade of pulmonary arteriosclerosis.

6. The occurrence of hemoptysis in a case of rheumatic heart disease may help in distinguishing between an Austin-Flint murmur and the murmur of aortic regurgitation, or in the diagnosis of mitral stenosis, in certain cases.

7. When hemoptysis occurs in rheumatic heart disease, only occasionally is it caused by something other than the heart disease.

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# THE FORM OF THE VOLUME PULSE IN THE FINGER PAD IN HEALTH, ARTERIOSCLEROSIS, AND HYPERTENSION

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THE pulse wave in the digital vessels was first recorded by Müller and Weis,<sup>1</sup> who mention the similarity between the radial and digital pulse wave forms. Bonsdorff<sup>2</sup> appears to have been the next to study the digital pulse wave. Although he did not make a comparative study of the digital and radial pulses, his tracings indicate that the digital wave is similar to the radial tracings of others. Uehata<sup>3</sup> made a comparative study of the radial and digital pulse wave forms but did not describe the technique which he used. His results are at variance with other, more detailed descriptions. Greven and Federschmidt,<sup>4</sup> who used plethysmographs with optical recorders, studied the velocity of the pulse wave from the radial to the digital arteries, and also the contours of the waves. Matthes, Gross, and Gopfert,<sup>5</sup> who used a photoelectric technique, investigated the forms of the simultaneously recorded radial and digital pulse waves. Goetz<sup>6</sup> recorded photoelectrically the contour of the digital wave alone.

That the contour of the peripheral pulse wave undergoes alterations in various conditions, such as fever, chronic nephritis associated with elevated blood pressure, and arteriosclerosis, has been appreciated by every investigator who has recorded pulse waves and was recognized even before the waves were recorded. In a general way, the alterations which occur in the wave contour have been described. It is well known that the pulse becomes more dicrotic during fever, and that, in arteriosclerosis, the secondary waves on the aortic limb (see below) become obliterated, and the peak of the wave becomes rounded. Until the work of Matoba,<sup>7-9</sup> no systematic attempt had been made to differentiate the genesis of the arteriosclerotic, or high pressure, pulse from that of the normal pulse. Greven and Federschmidt, in their excellent article,<sup>4</sup> illustrated the transition of the normal pulse to the arteriosclerotic form, but did not investigate the matter further. Matthes, Gross, and Gopfert<sup>5</sup> found contour changes in their digital tracings, but failed to point out what relationship, if any, they observed between the tracings from subjects with abnormal, and those with normal, vascular dynamics, although they promised to develop this point in a later paper.

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Judging from these citations from the literature, from many published finger plethysmograms, and from an extensive personal experience with photoelectric plethysmography of the skin, one finds it obvious that the propagation of the pulse wave into the smallest arteries presents problems in circulatory dynamics which are worthy of systematic exploration. This paper presents data on the form of the volume pulse of the finger pad, on the time relations between the components of the pulse wave, and on the relations between these measurements and similar simultaneous observations on the radial pulse. The data were obtained on healthy subjects and also on patients with hypertension and arteriosclerosis.

The volume pulses of the finger pad and radial artery were selected for study for several reasons: (1) They lend themselves well to our plethysmographic technique. (2) Of all of the peripheral vascular areas in man, the finger vessels have been most studied. This furnishes a background of understanding which is not available in the case of such other areas as the ear, forehead, and forearm. (3) Records of the volume pulses in the ear, forehead, and nasal septum, made by ourselves and others,<sup>5</sup> have shown such a striking difference in form that they constitute a separate problem. It therefore seemed best to limit this study to the finger vessels and to learn what we could about them with our technique before extending the study to other, less well-understood areas.

#### METHODS

The volume pulses of the finger pad were recorded with photoelectric plethysmographs, the technical details of which have been previously described.<sup>10-15</sup> This method depends on the fact that, when a tissue is transilluminated, its opacity varies directly with its blood content. Each pulse effects a change in the blood content which depends on the capacity of the vessels, on the resistance encountered, on the degree of vasoconstriction or vasodilatation, on the elastic properties of the vessels, and possibly also on the elastic properties of the tissues surrounding the vessels. The resulting volume pulses are most conveniently recorded by the photoelectric technique. It is not known with any certainty whether there are volume pulses in the arteries, arterioles, capillaries, or veins. It is possible that looping of the small arteries with each pulse<sup>16</sup> may be the source of the volume changes which are recorded as volume pulses. Important as these questions may prove to be with respect to the interpretation of the data in this paper, it seems probable that, irrespective of how the volume pulses are actually generated in a small portion of tissue such as the finger pad, they do portray, among other things, small artery behavior. This interpretation is placed upon them here; it is subject to the indicated reservations, which we plan to explore later.

In recording the pulse wave in the larger arteries with the photoelectric plethysmograph, the instrument is brought into firm contact with the skin directly over the vessel. The form of the pulse wave in the larger vessels is not affected by the pressure exerted by the holder unless the pressure is excessive. The contour may be accurately recorded even when the instrument is several millimeters from the skin surface, but direct application is preferable because it reduces the possibility of motion of the area and skin in relation to the light. Motion grossly distorts the record. Its effects are easily recognized. The presence of a small volume pulse in

the skin vessels directly over the large artery does not affect the record of the larger pulse because the latter is enormously larger than the former. It takes but little practice to learn when the arterial pulsations are being recorded properly, for the pulsations decrease rapidly when the plethysmograph is placed on either side of the vessel. They are recorded easily only when the plethysmograph is directly over the vessel, unless the amplification is increased considerably. Other sources of error have been discussed elsewhere.<sup>10, 11</sup>

The radial and finger pad pulses were registered simultaneously by means of a constant-speed camera; a Cambridge string galvanometer and a General Electric tension galvanometer (type A1) were used as the recording instruments for the majority of the records. Both of these respond to frequencies well above the minimal level required (Wiggers<sup>17</sup>) to record the peripheral pulse accurately. The light beams were adjusted to eliminate parallax.

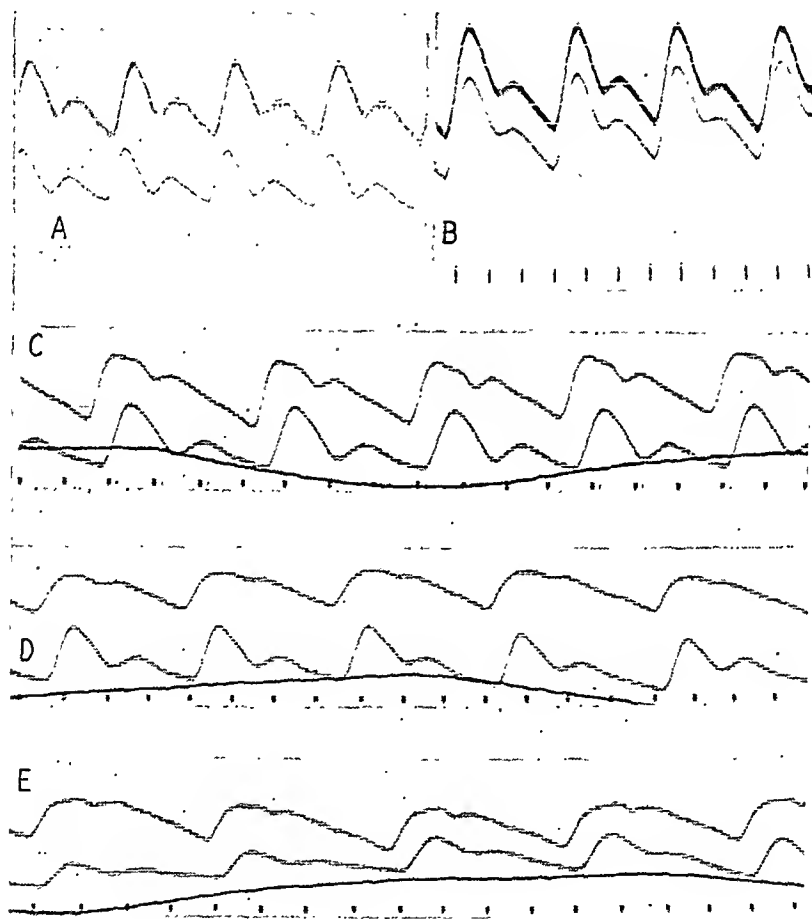


Fig. 1.—A, Comparison of the volume pulses of the finger pad (upper record), recorded photoelectrically, and of the terminal portion of a neighboring finger (lower record), recorded optically with a mechanical plethysmograph. Analysis of the two records by the method of Fig. 3 yields the same data; B, Volume pulses of thumb pad. Upper record obtained with capacity-coupled amplifier, lower record with resistance-coupled amplifier. Time, 0.2 sec.; C-E, Skin volume pulses. Time, 0.2 sec. Respiration (R) recorded by pneumograph. Lower volume pulse in each figure is from the finger pad. C, Upper record, from ear lobe; D, upper record, from forehead; E, upper record, from side of nose.

The size of the recorded pulse waves is arbitrary; it depends on the amplification employed. We used amplification sufficient to render detail apparent. It has been our practice to make the digital pulse somewhat larger than the radial.

The validity of a study of this kind depends on the adequacy of the method used. The ability of the photoelectric plethysmograph to follow vascular reactions

has been carefully compared with that of accurate mechanical plethysmographs.<sup>11</sup> The photoelectric records of the radial pulse are indistinguishable from those made with accepted optical methods. The accuracy of optical registration of the volume pulse of the terminal phalanx of the finger by means of a mechanical plethysmograph is theoretically open to question because of the periodicity of the system. However, such records, when properly made, compare well with the photoelectric records (Fig. 1A). The fact that the photoelectric technique eliminates errors caused by inertia and uses recorders of a high frequency makes it preferable to all others. In addition, this method permits flexibility in the adjustment of sensitivity without loss in frequency of response, and also allows the subject to take a natural relaxed position. The instrument is brought to the subject, not the subject to the instrument.

Since these records were made with capacity-coupled amplifiers,<sup>14</sup> which were used simply because they were convenient, it seemed wise to compare them with others which were made with resistance-coupled amplifiers whose adequacy had been previously established.<sup>11, 12</sup> Fig. 1B presents a comparison. The pulses were recorded with a plethysmograph specially constructed for the purpose. Two photoelectric cells were used separately and simultaneously to record the pulses in the same skin area, which was illuminated by a common light. The two records were identical.

Each subject was seated in an armchair; the right arm was comfortably flexed and placed on a support which also carried the photoelectric plethysmographs. The subject was allowed to rest for one-half hour before a record was made. Usually, two or three short records were taken at intervals of five to ten minutes. Brachial blood pressures were measured by the usual auscultatory method. Theoretical considerations indicate that it is desirable to have subjects in the basal state. However, in the case of the normal subject, the form of the finger volume pulse is not significantly different when the subject is asleep on a comfortable cot, nor is it affected by position (sitting or lying). "Crest times" (see below) remain unchanged. Also, preliminary observations indicated that variations in the tone of the finger vessels which occur as a result of "spontaneous" waves of psychic or thermoregulatory origin have little effect on the form of the volume pulse. It therefore seemed more practicable to make the observations under the conditions indicated here, with the subject in the so-called "resting" state. Most of the records were made at least two hours after eating. The room was comfortably warm (26° to 28° C.) and quiet. The subject was requested to relax as much as possible in order to minimize the influence of psychic vasomotor stimulation. The technique was explained to the subject in detail, in order to decrease the apprehension that many persons have with regard to strange procedures.

#### MATERIAL

The normal subjects included 115 young, healthy, male, medical students and members of the faculty; their ages ranged from 20 to 45 years. The subjects with arterial disease, who numbered forty-three, were recruited from the student body, faculty, and the vascular clinic of the Firmin Desloge Hospital. Their ages ranged from 22 to 75 years. Normal subjects were defined as obviously healthy persons whose blood pressures were less than 120/80 on several occasions, who had no demonstrable heart disease, who were normal or hypo-reactors to the Hines-Brown cold-pressor test, and who had no palpable sclerosis of the brachial artery or visible sclerosis of the retinal vessels.

No patients with aortic or mitral valve lesions were included in our series. Some of the hypertensive patients had rather severe cardiac damage, but all were ambulatory. Patients with marked disturbances in cardiac rhythm were excluded.



## RESULTS

*A. Normal:*

Typical differences in the form of the volume pulses in several areas (forehead, side of nose, lobe of the ear, finger pad) are shown in Fig. 1C-E. Flattening of the summit of the primary wave and a higher position of the incisura are the main features which differentiate the volume pulses in these other areas from those in the finger pad and

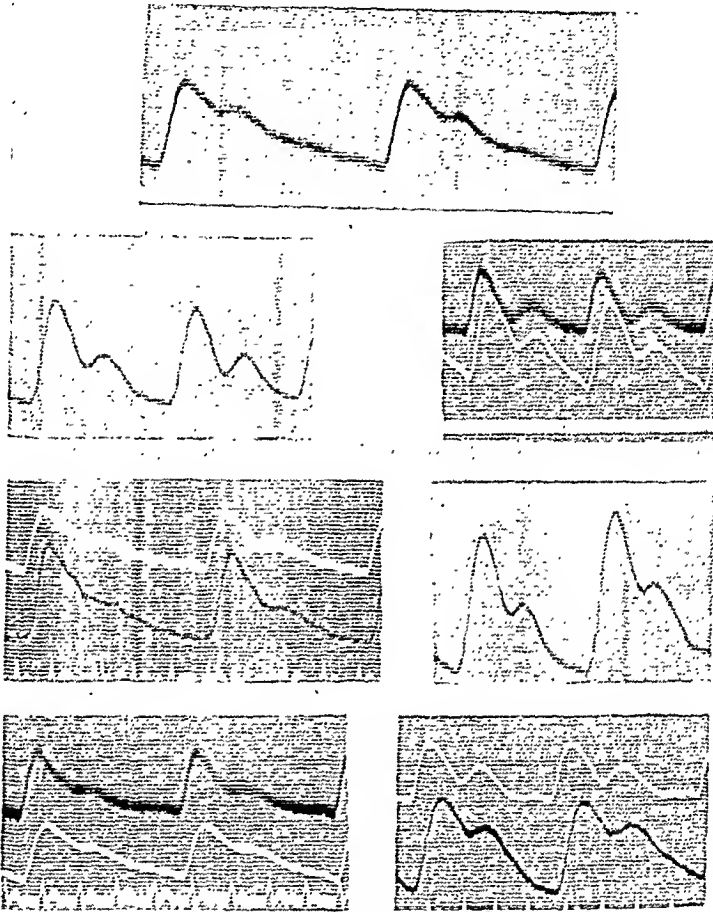


Fig. 2.—Normal finger pad and radial volume pulse tracings. Top record, radial; bottom, finger pad. Time, 0.2 sec.

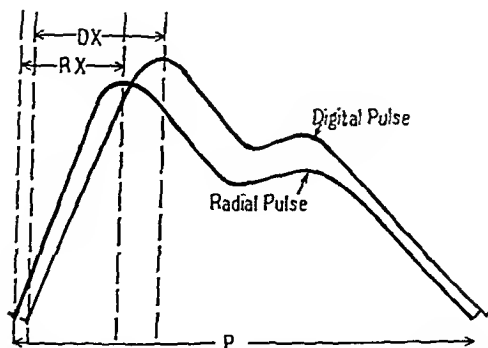


Fig. 3.—Method of analysis of the volume pulses. Primary wave is the anacrotic limb to its crest (see text for implied difficulties in ascertaining the position of the crest). DX, Digital pulse crest time; RX, radial pulse crest time; P, duration of pulse cycle.

radial artery. When crests are distinguishable, crest times are essentially the same as those of the pulse in the finger pad. Further description or analysis will not be attempted here.

It is apparent that the volume pulses of the finger pad and radial artery are grossly similar in normal subjects (Fig. 2). The method of detailed analysis of these and similar records is illustrated in Fig. 3. The method follows the procedure of Yamaguchi,<sup>18</sup> who calculated the duration of the ascent of the primary wave of the radial pulse in a large series of cases. He found significant differences between normal subjects and persons with hypertension and arteriosclerosis. We have called the duration of the ascent of the primary wave, the *crest time*.

TABLE 1  
DIGITAL AND RADIAL PULSE CREST TIMES IN NORMAL SUBJECTS

NO.	SUB- JECT	AGE (YR.)	RESTING BLOOD PRESS- SURE	PULSE RATE	RADIAL CREST TIME IN SEC.	DIGITAL CREST TIME IN SEC.	RADIAL CREST TIME AS % OF PULSE CYCLE	DIGITAL CREST TIME AS % OF PULSE CYCLE	DIFFER- ENCE BE- TWEEN RADIAL AND DIGITAL CREST TIMES IN % OF PULSE CYCLE
1	L. S.	35	112/75	72	0.130	0.150	15.0	17.1	2.1
2	R. J.	25	110/74	85	0.112	0.130	16.0	17.8	1.8
3	R. B.	21	108/74	60	0.118	0.138	10.2	11.9	1.7
4	W. O.	24	106/75	65	0.100	0.112	11.1	12.5	1.1
5	B. M.	23	112/70	69	0.118	0.118	13.5	13.5	0.0
6	J. D.	28	112/72	86	0.112	0.120	15.3	17.1	1.8
7	A. H.	42	108/72	77	0.104	0.132	15.5	18.4	2.9
8	C. W.	23	108/70	90	0.112	0.137	13.6	16.7	3.1
9	I. E.	25	99/75	92	0.088	0.100	13.5	15.4	1.9
10	G. B.	45	112/75	68	0.102	0.125	12.0	11.3	2.3
11	V. M.	23	103/72	80	0.112	0.130	14.7	17.0	2.3
12	F. G.	24	120/80	62	0.102	0.118	10.8	12.1	1.3
13	T. K.	22	90/65	75	0.118	0.132	14.7	16.6	1.9
14	B. H.	23	112/74	71	0.105	0.125	12.4	11.8	2.4
15	J. H.	22	108/65	75	0.107	0.131	13.9	15.2	1.3
16	J. K.	22	118/68	81	0.100	0.125	13.6	15.2	1.6
17	J. A.	30	110/74	77	0.123	0.148	15.7	18.7	3.0
18	R. M.	36	105/80	77	0.123	0.132	15.6	18.4	2.8
19	E. T.	22	118/78	80	0.125	0.142	16.6	19.0	2.4
20	R. H.	24	106/75	77	0.107	0.123	13.8	15.8	2.0
21	R. G.	22	110/68	77	0.113	0.138	14.5	16.8	2.3
22	N. T.	23	110/70	86	0.100	0.119	14.3	17.0	2.7
23	N. R.	24	110/70	88	0.106	0.113	15.6	18.0	2.4
24	V. S.	21	95/65	83	0.108	0.126	15.0	16.7	1.7
25	P. H.	21	110/60	66	0.087	0.108	11.1	13.6	2.5

The position of the crest or summit is easily recognized in records of the radial and finger pad pulses from normal subjects, and also in many cases of hypertension and arteriosclerosis. However, when the summit of the pulse wave is flattened or modified by small secondary waves (e.g., the *Zwischenschlag*) or by ascent of the incisura, it may be very difficult to identify the true crest of the primary wave (Fig.

1D-E). Decision in such cases may be arbitrary. Fortunately, the number of such instances in the case of the finger pad pulses is very small, but they are a regular occurrence in the case of the volume pulses of the skin of the head.

Our values for the radial crest times (Table I) on normal subjects agree with those of Yamaguchi. The crest time for the volume pulse of the finger pad is slightly longer than that of the radial (Table I).

It is convenient to express the crest time in per cent of the duration of the total pulse cycle. When this is done, it is found that the radial crest time normally is between 10 and 16 per cent of the pulse cycle, and the digital crest time from 0 to 4 per cent longer; the most frequent difference between the two is from 1 to 3 per cent (Table I). In no case was the digital crest time shorter than the radial. It should be noted that these calculations are based upon average pulse wave duration during one complete respiratory cycle; the wave undergoes slight variations during respiration.

This relation between the duration of the primary waves (Hauptgipfel) of the radial and digital pulses is the reverse of that between the subclavian and cubital pulses. It is generally known that, in the more central arteries, the crest of the wave travels more rapidly than its base. As a result, the crest gains on the base, and the crest time shortens as the wave proceeds along the artery. Increased resistance, however, has an opposite effect, in that it slows the propagation of the crest of the wave.<sup>19</sup> It is possible, therefore, that the usual delay between the peaks of the radial and digital primary waves ("crest times") is the result of a slightly elevated resistance peripheral to the radial artery.

In comparing normal radial and digital volume pulses, one notes that the incisura occurs uniformly higher on the cataerotic limb of the digital wave than on that of the radial. The height of the incisura varies during a respiratory cycle; it is higher on the cataerotic limb during expiration. There is a similar variation in the height of the incisura of the radial pulse during the respiratory cycle.

The incisura tends to be higher on the cataerotic limb as age increases, but this is not necessarily so. An attempt to find a relation between age and the relative height of the incisura met with failure. The tendency of the incisura to rise on the digital wave when constriction of the finger vessels occurs may be an important reason for our inability to obtain a correlation between its relative position and age. The tonus of the finger vessels is extremely labile; it varies as a result of thermoregulatory requirements, psychic influences, noises, etc. Constant conditions would be provided only by maximal dilatation, which is not readily obtained except by means of special techniques. It seems, however, that the height of the radial incisura is usually less than half that of the peak of the pulse, and that the digital incisura occurs at a variable height in excess of half that of the peak of the pulse.

Persons in the late thirties and forties may have the same wave form as younger subjects. Fig. 4 illustrates three such cases. The blood pressure in each case was below 120/80.

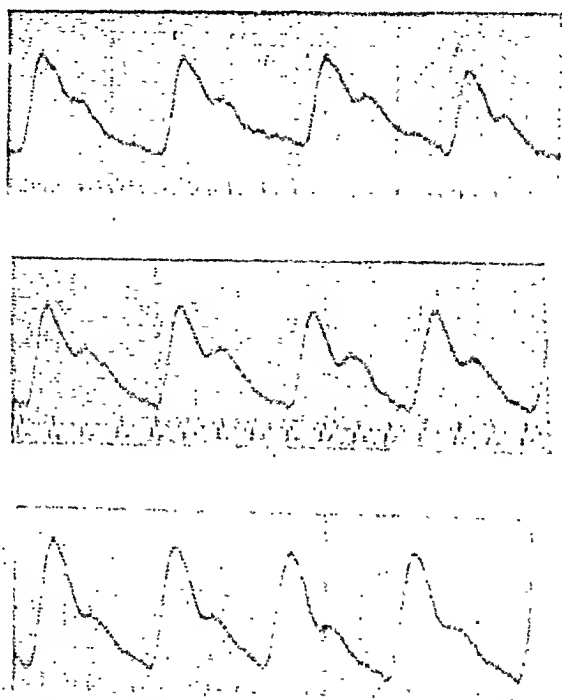


Fig. 4.—Normal finger pad and radial volume pulses. White record, radial; black record, finger pad. Time, 0.2 sec. Top figure from a man, 45 years old (G.B., Table 1); middle figure from a man, 42 years old (A.H., Table 1); lower figure from a man, 36 years old (R.M., Table 1).

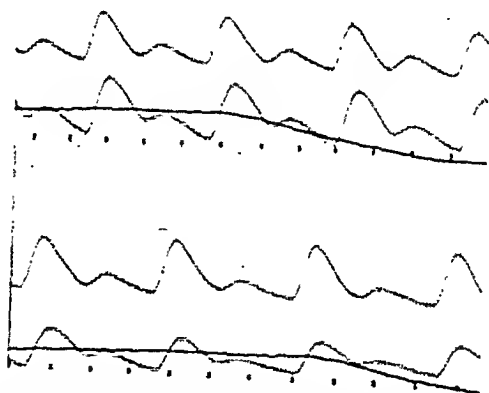


Fig. 5.—Effect of vasoconstriction in finger pad on the volume pulses of the radial artery (upper record in each figure) and of the finger pad (lower record in each figure). Figures are not continuous.

It was important, before trying to interpret records taken from obviously pathologic subjects, or from subjects who did not fit into our definition of normal, to try the effect of constrictor influences on the wave form in normal subjects. Fig. 5 illustrates the effect of immersing the opposite hand in water at 4° C. The constrictor effect is obvious, but there was no alteration in "crest time" nor in the fundamental form

of the wave. The effects of "psychic" constriction are similar to those produced by cold. It may be argued that such stimuli do not produce an adequate response, but we were not interested in the effects of complete obliteration of the lumina of the finger vessels, but only in the effects of a relatively moderate increase in tone. Many observations on "psychic" constriction, which occurs in practically every case when the camera is turned on, and lasts only a few moments, show that it produces no fundamental alteration of the form of the volume pulse in the radial and digital arteries of normal subjects.

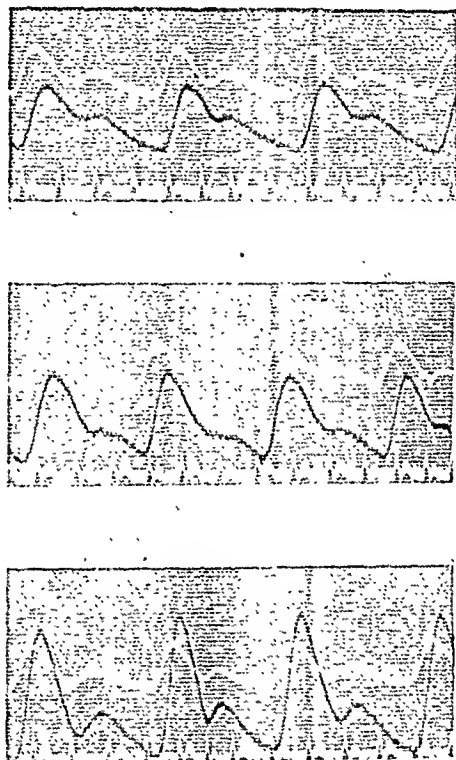


Fig. 6.—Effect of amyl nitrite on the volume pulses of the radial artery (white record) and of the finger pad (black record). Top figure before, middle figure during, and lower figure three minutes after administration of the drug. Time, 0.2 sec.

That moderate changes in the tone of the finger vessels do not influence the crest times of the finger pad volume pulses is further supported by the effects of amyl nitrite inhalation (Fig. 6). The increase in the dicrotism of both the digital and radial waves is evident. Similar effects were reported by Matthes, Gross, and Gopfert,<sup>5</sup> and by Mann.<sup>20</sup> Differences in the amplitude of the finger volume pulses in this record are arbitrary, for it was necessary to increase the amplification because of the constriction induced by administration of the drug, yet there is no significant difference in the fundamental form of the waves (excepting the dicrotism) or in the crest times in any of the records. It must be admitted that the circulatory action of this drug is extremely complex. The development of dicrotism in the finger pad pulses at the time when the finger vessels were constricting as a result of the sympathetic excitement induced by the drug poses an interesting problem.

A study of the crest times in relation to variations in resting heart rates (Table I) showed nothing important.

### B. Arterial Disease:

Yamaguchi<sup>18</sup> found that the crest time (time to the peak of the primary wave) was absolutely and also relatively proportional to the duration of the pulse cycle in certain types of vascular disease, such as nephrosclerosis, chronic nephritis, arteriosclerosis, and hypertension. That is by no means a new concept, but it had never been quantitated. We were interested in confirming his observations, in extending them to the digital pulse wave, and in studying any differentiating characteristics.

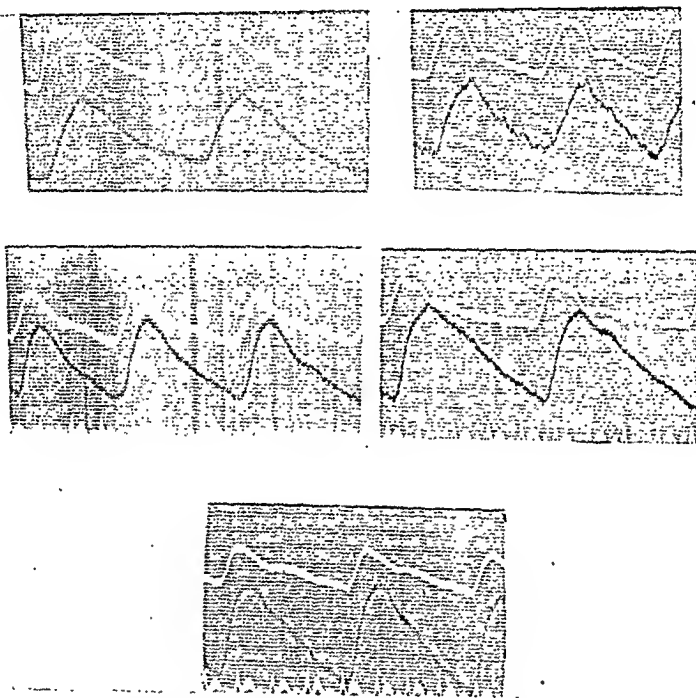


Fig. 7.—Volume pulses in arteriosclerosis without hypertension. Radial, white. Finger pad, black. Time, 0.2 sec. Top left figure: man, 78 years old (C.B., Table II). Top right figure: man, 75 years old (D.S., Table II). Middle left figure: woman, 34 years old, B.P. 120/80, severe nephritis several years previously; at the time records were made the urine was normal and there was no evidence of sclerosis in retina; radial crest time, 0.125 sec.; digital crest time, 0.16 sec. Middle right record: (J.P., Table II) no clinical evidence of arteriosclerosis. Lowest figure: medical student (W.M., Table II), hyper-reactor to cold-pressor test.

1. *Sclerosis*.—Records of the radial and digital volume pulses of two old men are shown in Fig. 7. The crest times in these cases were markedly increased. Both men had advanced arteriosclerosis (marked palpable sclerosis and tortuosity of main arteries; retinal arteries only slightly tortuous, with no broadening of light reflecting band). Their blood pressures were consistently below 120/80.

As the number of subjects studied increased, it became apparent that, in certain younger persons, changes occurred in the contour of the digital waves which were not apparent in radial tracings alone. These

younger subjects had normal blood pressures and showed no gross evidence of arteriosclerosis (either by arterial palpation or ophthalmologic examination), yet the digital wave form was fundamentally abnormal and resembled that of the older subjects (Fig. 7; note the increase in the digital crest times). For this reason we have placed these subjects

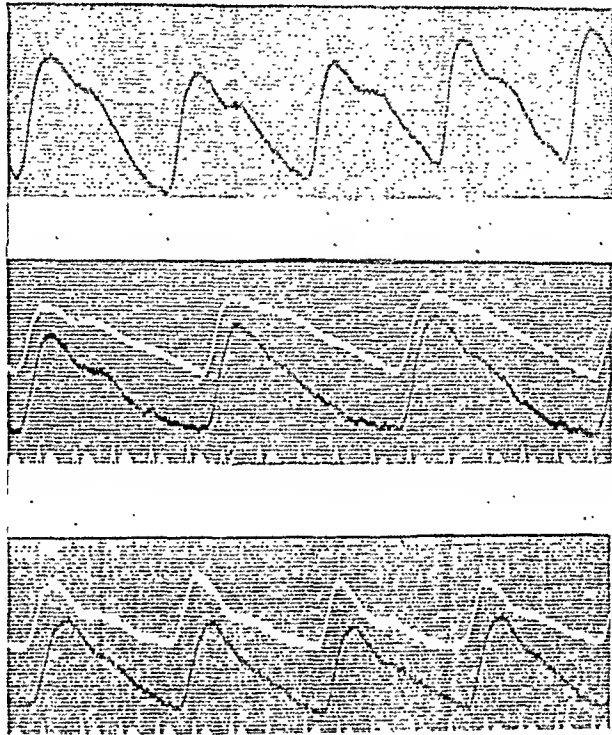


Fig. 8.—Volume pulses in subjects without clinical evidence of arteriosclerosis and with normal blood pressures. Radial, white; finger, black; time = 0.2 sec. Top figure: J.H., Table II. Middle figure: man, 47 years old, B.P. 112/75; radial crest time, 0.14 sec.; digital crest time, 0.21 sec. Lower figure: F.K., Table II.

TABLE II  
RADIAL AND DIGITAL CREST TIMES IN SUBJECTS WITH ARTERIOSCLEROSIS

NO.	SUBJECT	AGE (YRS.)	RESTING BLOOD PRESSURE	PULSE RATE.	RADIAL CREST TIME IN SEC.	DIGITAL CREST TIME IN SEC.	RADIAL CREST TIME AS % OF PULSE CYCLE	DIGITAL CREST TIME AS % OF PULSE CYCLE	DIFFERENCE BETWEEN RADIAL AND DIGITAL CREST TIMES IN % OF PULSE CYCLE
1	R. P.	22	110/64	95	0.100	0.125	13.9	19.6	5.7
2	N. M.	23	110/70	64	0.100	0.150	10.6	16.0	5.4
3	C. B.	78	120/70	84	0.175	0.205	24.6	28.8	4.2
4	F. M.	44	120/80	66	0.140	0.205	14.8	22.2	7.4
5	R. H.	25	88/54	77	0.087	0.133	11.7	17.7	6.0
6	W. M.	22	112/72	81	0.113	0.175	15.2	23.7	8.5
7	D. S.	75	118/75	72	0.118	0.213	14.2	25.6	11.4
8	J. P.	40	100/60	62	0.100	0.220	10.3	22.3	12.0
9	J. H.	40	110/70	90	0.094	0.150	14.2	22.6	8.4
10	F. K.	50	120/80	77	0.140	0.190	17.9	24.6	6.7

in the arteriosclerotic group, although the absence of other positive evidence should be emphasized. This does not mean that a more comprehensive examination of the arterial system (arteriography, etc.) would not have revealed arteriosclerosis.

Fig. 8 illustrates records from subjects who did not show arteriosclerosis on clinical observation (arterial palpation, opthalmologic examination). A comparison of these records with those of obviously arteriosclerotic subjects (top figures of Fig. 7) suggests either that the process of sclerosis is under way in the smaller vessels, or that changes in the elasticity of these vessels or of the tissues have proceeded far enough to alter the propagation of the pulse wave in the finger arteries.

One feature is common to all these subjects, namely, an increase in the crest time of the digital volume pulse. In all except the top record of Fig. 8, the incisura and the rebound wave which follows it have disappeared from the finger pulses. The contour of the radial volume pulse shows considerable variation. In the top record of Fig. 8 and the bottom record of Fig. 7 the radial pulses are normal in appearance; the remainder of the radial pulses show changes in contour which have been generally ascribed to arteriosclerosis. These changes may also occur in subjects who have no clinically recognizable arteriosclerosis.

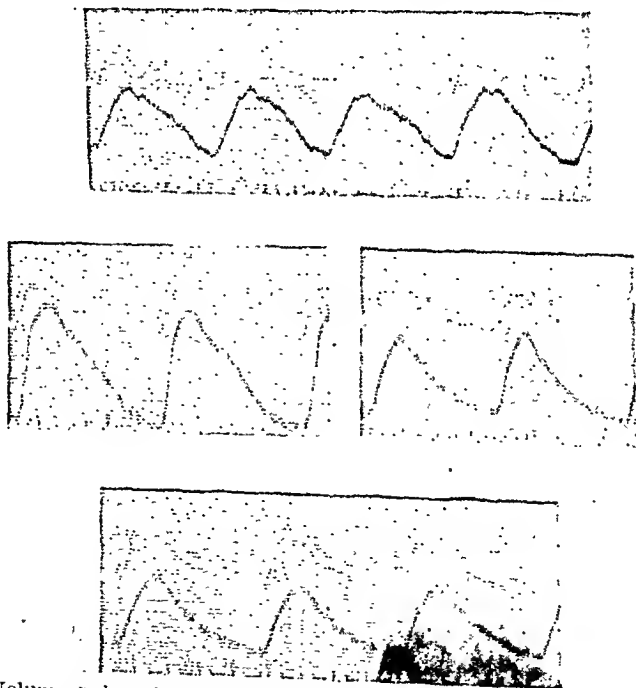


Fig. 9.—Volume pulses in subjects with hypertension. Radial, white; finger pad, black. Time, 0.2 sec. Top figure: L.C., Table III. Middle left figure: A.M., Table III. Middle right figure: H.S., Table III. Lowest figure: N.S., Table III.

2. *Hypertension*.—Records taken from patients with hypertension are illustrated in Fig. 9. The similarity between the records from patients with hypertension (Table III, Figs. 9 and 10) and those from patients with arteriosclerosis, but without hypertension, is obvious (Table II,



Figs. 7 and 8). An increase in crest time, loss of the rebound wave in both the digital and radial pulses, triangulation of the digital pulse, and rounding and flattening of the radial pulse are common to both groups. All records from patients with fairly long-standing hypertension presented similar features.

An interesting case of malignant hypertension is presented in Fig. 10 (A.B., Table III). The patient complained of headaches, dizziness, weakness, and dyspnea. Ophthalmologic examination revealed very tortuous arteries which branched at right angles and had broad light reflexes. Some of the arterial branches were markedly constricted. The nonprotein nitrogen content of the blood was 45 mg. per cent. She had had a bilateral lumbar sympathectomy and splanchnicotomy three years before we made our observations. The abnormalities in the contour of

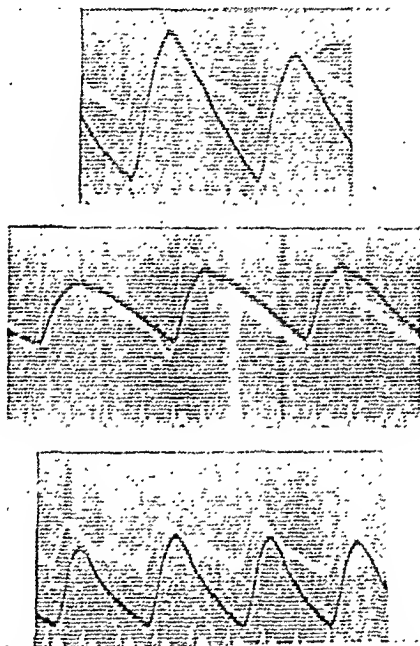


Fig. 10.—Volume pulses in a case of malignant hypertension (A.B., Table III). Radial, white; finger pad, black. Time, 0.2 sec. Top figure, "resting" record. Middle figure, during "psychic" vasoconstriction. Lowest figure, after amyl nitrite.

her radial and digital volume pulses are obvious in the top record. In the middle record one sees the effect on the form of the pulse of a constriction of psychic origin. The most significant thing was the appearance in the radial record of a notch and wave which were grossly similar in position to the normal rebound wave; they disappeared when the digital vessels relaxed. It is interesting to note that there was no change in the crest time. This record suggests that reflection of waves from the periphery may contribute to the formation of the radial wave. The bottom record shows the effect of amyl nitrite on the contour of the waves. There was no fundamental alteration. The crest times were shortened absolutely, but not relatively in proportion to the duration of the pulse cycle.

TABLE III  
RADIAL AND DIGITAL CREST TIMES IN SUBJECTS WITH HYPERTENSION

NO.	SUB- JECT	AGE (YRS.)	RESTING BLOOD PRES- SURE	PULSE RATE	RADIAL CREST TIME IN SEC.	DIGITAL CREST TIME IN SEC.	RADIAL CREST TIME AS % OF PULSE CYCLE	DIGITAL CREST TIME AS % OF PULSE CYCLE	DIFFER- ENCE BE- TWEEN RADIAL AND DIGITAL CREST TIMES IN % OF PULSE CYCLE
1	P. S.	40	180/110	80	0.075	0.125	10.7	16.7	6.0
2	S. S.	40	190/110	77	0.163	0.237	21.0	30.6	9.6
3	A. B.	27	185/110	92	0.217	0.242	27.6	30.4	2.8
4	L. K.	34	130/80	76	0.125	0.160	19.2	24.6	5.4
5	L. M.	24	140/110	88	0.087	0.113	12.9	18.2	4.3
6	J. S.	23	125/70	77	0.087	0.119	11.1	15.1	4.0
7	B. D.	47	235/135	100	0.125	0.147	20.0	24.0	4.0
8	N. S.	53	200/100	67	0.117	0.225	13.1	25.0	11.9
9	J. G.	23	140/86	77	0.123	0.188	15.8	24.2	8.4
10	J. W.	50	188/112	96	0.130	0.149	20.4	23.6	3.2
11	L. C.	40	210/120	77	0.085	0.225	11.0	28.8	18.8
12	A. M.	54	200/110	80	0.113	0.187	13.6	22.7	9.1
13	H. S.	60	170/110	77	0.087	0.188	11.2	24.0	13.8
14	N. S.	53	200/120	67	0.118	0.225	13.1	25.0	11.9

Yamaguchi<sup>18</sup> and Matoba<sup>7</sup> showed that an increase in radial crest time in arterial disease is not caused by bending or breaking of the primary wave, but by accentuation of a small wave between the peak of the primary wave and the incisura which they call Zache II. Greven and Federschmidt<sup>4</sup> and Matthes, et al.,<sup>5</sup> showed that this wave was the cause of the increase in crest time in both the radial and digital pulses. They call this wave the *Zwischenschlag*. This wave may or may not be visible in the sphygmograms of normal persons. When it is present, it is very small (Fig. 2, third row left, radial; Fig. 4, top, radial). These authors are of the opinion that increased peripheral resistance is responsible for the augmentation of this wave. Judging from various records which are not shown, one finds it probable that the augmentation of the *Zwischenschlag* is responsible for the increase in radial and digital crest times. The relation of this wave to the increase in crest time is clearest in young subjects, or when the alteration in vascular dynamics is not of long standing. Presumably, the factor of organic change in the vessel walls determines whether the wave can be recognized.

The vibrations on the anacrotic and catacrotic limbs of the digital pulses in the upper right record of Fig. 7 and the upper record of Fig. 9 may have originated in the vessel wall and have been caused, in part, by resistance. They are not instrumental in origin. They usually occur regularly in persons who show them. They diminish with a decrease, and increase with a rise, in the tone of the vessels; the change in tone is indicated by the amplitude of the volume pulse. The vibra-

tions may increase on the digital wave, with restoration of the radial contour to its fundamental form. They do not possess a regular frequency, but may be compared to audible "noise." They are usually absent in young, normal subjects, but they have appeared in several cases of hyper-reactors to cold who had increased tonus of the digital vessels; they disappeared, during rest in bed, from the digital pulse of a young girl with hypertension, and reappeared when she resumed her occupation. It is possible that some of these vibrations may have their origin in fine tremors. Their significance is not clear.

#### DISCUSSION

The pulse wave data presented in this paper suggest that the *effects of arteriosclerosis and hypertension on the dynamics of the arterial system appear in the vessels of the finger pad before they do in the radial artery*. In our series of records showing alterations in the contour of the radial pulse there have always been changes in the digital pulse, as well, but these were not always accompanied by alterations in the simultaneously recorded radial pulse (Fig. 7, bottom record; Fig. 8, top and bottom records). Further evidence in support of this statement is found in the fact that changes in the radial pulse may be less marked than those in the simultaneously recorded digital pulse (Figs. 7, 8, and 9). These observations suggest that the contour of the digital pulse is a better indication of the condition of the peripheral arteries than is the contour of the radial pulse. It is apparently impossible to predict with accuracy the contour of the digital pulse from the contour of the radial pulse in subjects with altered arterial dynamics.

Interpretation of the origin of the alterations in digital pulse contour in arteriosclerosis requires a detailed correlation between the pulse contour and other objective signs, such as radiographic data and vasodilator tests. This has not yet been attempted. However, there was neither palpable sclerosis of the main arteries nor sclerosis of the retinal arteries in our younger subjects (Fig. 7, middle and bottom rows; Fig. 8), but these subjects showed the same changes in the digital pulse that occurred in subjects with recognizable sclerosis (Fig. 7, top row).

The rebound wave (following the incisura) in the digital pulse tends to disappear in subjects with increased arterial pressure (Figs. 9 and 10). This has also been observed by Matoba<sup>7</sup> and Greven and Feder-schmidt.<sup>4</sup> The exact cause of the loss of the rebound wave is not known. It may be that, in young persons with hypertension, the rebound wave is damped by interference with other reflected waves. In patients with more severe and long-standing hypertension, it is possible that the smoothing of the digital wave, with loss of all evidence of secondary waves, is caused by organic changes in the vessel wall (Figs. 9 and 10). Tending to confirm this opinion is the type of digital wave which occurs in subjects with sclerosis but without hypertension (Fig. 7).

It is possible that the differences between the normal radial and digital pulse waves are caused by a slight increase in peripheral resistance as the pulse wave passes from the radial artery. It is difficult, if not impossible, to attribute the differences between these two waves in subjects with arteriosclerosis and with hypertension to increased peripheral resistance alone, for moderate, and even marked, increases in the tone of the finger vessels fail to produce these differences in normal subjects.

We are uncertain as to the location of this resistance. It may be in the digital arteries or in the small arteries and arterioles of the finger pad. Additional observations bearing on this question are: (1) the diastolic pressure in the vessels of the volar arch usually exceeds that in the radial artery;<sup>2</sup> (2) the pulse wave velocity diminishes between the radial artery and the digital vessels;<sup>4, 5</sup> (3) constriction of the finger vessels produced by vasomotor reflexes (see above) does not alter the digital crest times in normal subjects. These facts might be considered as indicating that the resistance which is responsible for the slight prolongation of digital crest time is located in the digital arteries. The extent of their participation in moderate vasoconstrictor reflexes has not been ascertained. If experience in comparing radial artery and finger pad artery reactions<sup>13</sup> can be used as a guide, the digital arteries did not constrict while the vasomotor reflexes were acting. In the absence of direct evidence, this is consistent with the fact that the digital crest time was not affected by constriction in the pad.

A reasonable interpretation of the data in this paper is possible along the following lines: The fact that the arteries act as an elastic reservoir is well known. Greven and Federsehmidt<sup>4</sup> have suggested that there may be two reservoirs, a central and a peripheral. The peripheral elastic reservoir is postulated as beginning somewhere peripheral to the radial artery. They suggested this because of their observation that the pulse wave velocity in the radial-digital span is less than it is in the brachio-radial span. They are of the opinion that this would not be so if the entire arterial system acted as one elastic reservoir. Matthes, Gross, and Gopfert<sup>5</sup> made similar observations and are of the same opinion as Greven and Federsehmidt. They make the further suggestion that this peripheral elastic reservoir has lower elastic limits than the central one. Neither group was able to define the anatomic limits of this theoretical reservoir. The alterations in wave form which occurred in our subjects with hypertension (Figs. 9 and 10) and with arteriosclerosis (Figs. 7 and 8), and the discrepancies between the radial and digital pulse contours in the younger subjects with these abnormalities (Fig. 7, bottom) further support the idea that there is such a system.

If the existence of a peripheral elastic reservoir be admitted, the normal and pathologic digital pulse contours may be explained as follows:

1. *In normal subjects the pulse wave meets with slight resistance upon entering the arteries peripheral to the radial, namely, the volar arch, digital arteries, and finger pad arteries.* This is indicated by the slight increase in crest time of the digital pulse (Table I). In normal persons the capacity of the elastic reservoirs made up by these arteries is sufficiently great that moderate constriction (the exact arterial participation cannot be defined, Fig. 5) does not cause alterations in the fundamental pulse contour or crest times. For this reason one does not obtain evidence for the presence or absence of such an elastic system from the pulse contours of normal subjects. (Matthes, et al.,<sup>5</sup> show several records of digital pulses which they say were obtained from normal subjects. From our data we would classify them as abnormal. They use these records as evidence that there is a peripheral elastic reservoir, but give no information as to what they consider normal records.

2. Accepting the possibility that the peripheral reservoir is less elastic than the central, it is *also possible that alterations affecting the properties of the vessel walls, such as arteriosclerosis or hypertension, would first become apparent in the peripheral reservoir.* This would explain two observations: first, that the digital wave form may be altered to a greater degree than the radial wave form; and, second, that alterations in the digital wave form are not necessarily accompanied by alterations in the radial wave form. It would seem that the latter phenomenon is accounted for by greater elasticity of the radial artery, for more perfect reflection of waves of peripheral origin would be expected in cases of hypertension and arteriosclerosis if the elastic properties of the vessels were the same. It seems probable that alterations in the radial pulse contour occur either when reflection from the periphery is sufficiently great to overcome this difference in elasticity, or when the elastic properties of the radial artery have been reduced by sclerosis.

Although the data in this study constitute indirect and inconclusive evidence, they suggest the possibility that changes in the finger pad pulses may be a very early indication of loss of elasticity of the arteries contributing to the propagation and modification of the pulse in the pad. The role played by the larger arteries of the hand (volar arch, digital arteries) and the small arteries and arterioles of the finger pad with respect to the form of the volume pulse in the pad has not been ascertained. This point is of importance to the objective of this study, for it had been hoped that recording the pulse wave in the minute arteries would help in the diagnostic evaluation of their condition. The data which have been obtained promise to aid in this attempt.

## SUMMARY AND CONCLUSIONS

1. The volume pulses in the finger pad and radial artery were studied by means of previously described photoelectric plethysmographs.
2. The normal digital pulse has essentially the same contour as the normal radial pulse.
3. In normal subjects, the interval between the base and the peak of the digital pulse wave, which we have termed the "crest time," is slightly greater than that of the radial pulse wave. The fact that the crest time of the digital pulse wave is longer than that of the radial suggests that the pulse encounters slightly increased resistance in the vessels of the hand and finger.
4. In arteriosclerosis and hypertension, the contour of the digital pulse is altered earlier and to a greater extent than that of the radial pulse. This change in contour results in an increase in crest time, accompanied by obliteration of the incisura and rebound wave. In young persons with hypertension, and in some subjects with hypertensive tendencies, irregular vibrations are present on the cataerotic limb of the digital pulse. They are less common on the radial pulse. The changes which occur in the contour of the digital pulse are always greater than those in the radial.
5. In hypertension and arteriosclerosis it is not possible, because of discrepancies in the alterations which take place in the waves, to predict from the radial pulse contour what the digital pulse contour will be.
6. Study of the form of the digital pulse does not enable one to differentiate arteriosclerotic changes in the finger vessel wall from those produced by hypertension, if the hypertension is of long standing.
7. The differences between the digital and radial pulse contours are probably caused by a difference in the elastic properties of the vessels, as has been suggested by others. This difference is not apparent in the pulses of normal subjects, but becomes evident in cases of arteriosclerosis and hypertension in which the normal arterial dynamics are altered.
8. The suggestion is made that the form of the finger pad pulse may contribute information on early changes in the elasticity of the arterial system which influence this pulse.

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# SPONTANEOUS VOLUME CHANGES IN THE EXTREMITIES

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VARIATIONS in hand volume, apparently spontaneous in nature, have been described by various authors.<sup>1-3</sup> The significance of these changes, however, has not been adequately analyzed. Since some doubt has recently been cast upon the view that changes in the volume of an organ are directly related to alterations in blood flow,<sup>4, 5</sup> it was thought worth while to investigate the spontaneous variations in limb volume, in the hope that more information might be gained as to the mechanism involved.

## METHOD

Eighty-one experiments were performed on forty-seven normal subjects whose ages ranged from 12 to 74 years. The plethysmographic method was used, with the technique previously described.<sup>1, 6</sup> The room temperature varied between 25 and 27° C., and the temperature of the water in the plethysmograph (bath temperature) was generally 32° C. In some instances, readings were obtained at bath temperatures of 19° and 45° C. In most experiments a contralateral hand and forearm, or hand and leg, were investigated simultaneously. The foot was studied in a number of cases. Special precautions were taken to eliminate external stimuli, and the subject was encouraged to relax mentally and physically. In some instances, the experiments were performed during sleep.

A base line was obtained by raising the Brodie's bellows to a mid-position, and limb volume changes were recorded on a slowly moving drum. The variations were calculated in cubic centimeters of increase or decrease per 100 c.c. of limb volume, using the base line, when it was temporarily maintained at a steady level, as a point of reference. For the purpose of tabulation, the results were divided into four groups: (1) marked variations (more than 0.6 c.c. per 100 c.c. of limb volume), (2) moderate variations (varying from 0.2 to 0.6 c.c.), (3) slight variations (less than 0.2 c.c.), and (4) no changes (constant base line). In a number of experiments the rate of blood flow was also measured.

In the case of the forearm and the leg, volume changes and blood flow readings were recorded with a pressure of 250 to 300 mm. Hg applied to the wrist and the ankle respectively, in order to eliminate all influences of vascular changes in the hand and foot.<sup>7</sup> In a few instances, base lines were obtained without this pressure. In the case of the hand, the effect of an elevation of venous pressure upon the spontaneous volume changes was investigated on numerous occasions. This was accomplished by maintaining a pressure of 70 to 80 mm. Hg either at the arm or forearm until the pressure in the veins of the hand had reached approximately the same level, and then recording a base line under these conditions.

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## RESULTS

## 1. Volume Changes in the Hand.

*A. Bath Temperature of 32° C.*—The hand was studied in forty-three subjects, and in a number of these the experiments were repeated from one to nine times. Spontaneous variations in limb volume were portrayed by sudden rises and falls of the base line, which varied in amplitude and occurred in an inconsistent and unpredictable fashion (Figs. 1 and 2*B*). A relatively constant level was maintained for only short periods at the crests and troughs of the waves. Simultaneous base line observations on the two hands revealed that the variations in

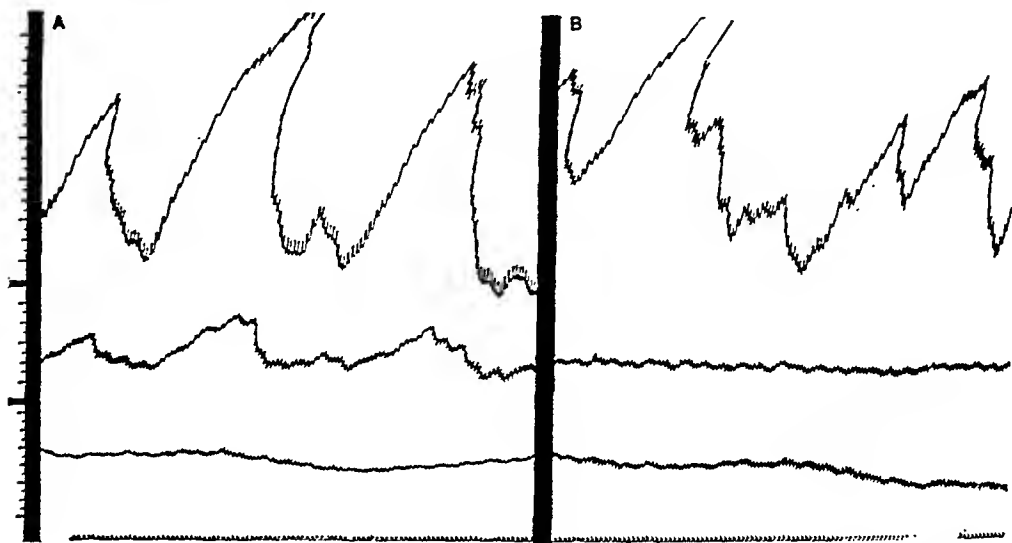


Fig. 1.—Spontaneous volume changes at a bath temperature of 32° C. and room temperature of 25° C. Subject, L.K. *A.* Upper curve shows spontaneous variations in hand volume; middle curve, spontaneous variations in forearm volume which occurred without applying pressure at the wrist; bottom curve, constant leg volume with no pressure applied at the ankle. *B.* Upper curve, hand volume, same as in *A.*; middle curve, constant forearm volume with a pressure of 300 mm. Hg at the wrist; bottom curve, constant leg volume with a pressure of 300 mm. Hg at the ankle. Time in seconds. Calibrations in 0.25 c.c.

volume were synchronous in the two extremities. Since the degree of spontaneous volume changes was found to be fairly constant from time to time in any one subject, it was possible to classify the results of the different experiments as follows: marked variations, twelve subjects; moderate variations, eleven subjects; slight variations, four subjects; and no variations, sixteen subjects. Of the twelve subjects with marked variations, eleven were in the second and third decades and one in the early part of the fourth decade. Seven of the eleven subjects who had moderate variations were between 19 and 35 years of age, and the remaining four were beyond the fourth decade. Of the four with slight variations, two were less than 35 years of age and two were elderly persons. Eleven of the sixteen subjects with no spontaneous variations were in the fourth to the eighth decades, and the remaining five were under thirty years of age.

B. *High and Low Bath Temperatures.*—In sixteen experiments the hand was exposed to a bath temperature of  $45^{\circ}\text{C}$ . Whereas in every instance the base line had previously exhibited marked or moderate variations at  $32^{\circ}\text{C}$ ., it was now maintained at a constant level (Fig. 2C), except in one instance. At a bath temperature of  $19^{\circ}\text{C}$ . there were no variations, or, at most, only slight changes (Fig. 2A).

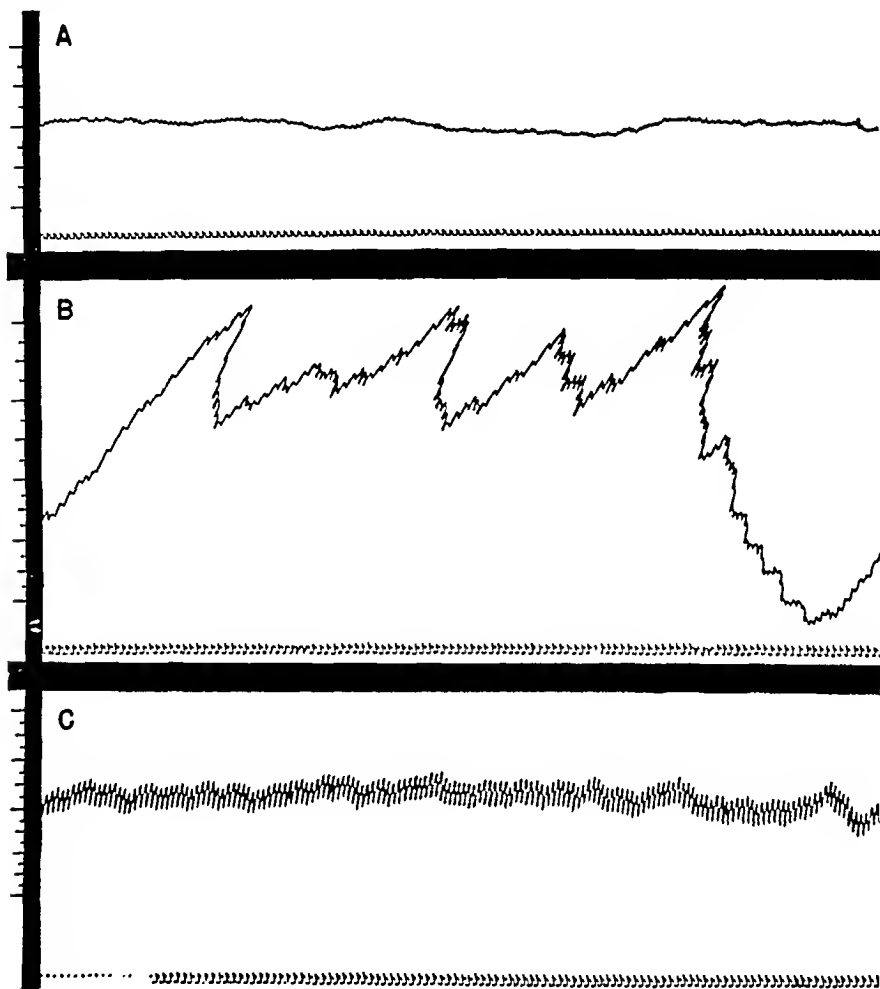


Fig. 2.—Effect of various bath temperatures upon magnitude of variations in hand of subject, D.A. A,  $19^{\circ}\text{C}$ .; B,  $32^{\circ}\text{C}$ .; C,  $45^{\circ}\text{C}$ . Room temperature,  $26^{\circ}\text{C}$ . Calibrations in 0.25 c.c. Time in seconds.

C. *Effect of Sleep at Bath Temperature of  $32^{\circ}\text{C}$ .*—Hand volume changes during sleep were studied in five subjects who showed a constant base line while awake. The response in the case of one young normal adult was typical, and is of particular interest because he was one of the few in his age group whose base line was steady. However, when he fell asleep during the course of the experiment, spontaneous variations in the volume of the hand appeared, and differed in no way from those which occurred in other young subjects (Fig. 3B). In the remaining four subjects, who were in the fourth to the sixth decades,

variations in hand volume were also observed during sleep, but the response was not as marked as in the case of the young adult. When the subjects awoke, the magnitude of the spontaneous volume changes usually decreased, but, as a rule, the base line remained somewhat less constant than before sleep occurred.

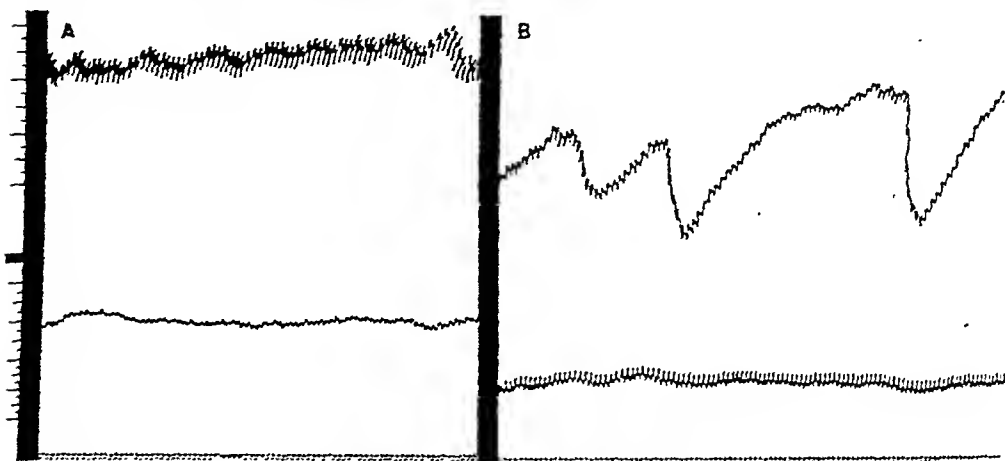


Fig. 3.—Effect of sleep upon spontaneous volume changes in hand of subject, L.W. A, Subject awake. Upper curve, constant hand volume; lower curve, constant forearm volume. B, Subject asleep. Upper curve, spontaneous variation in hand volume now present; no change in volume of forearm. Bath temperature,  $32^{\circ}$  C. Room temperature,  $26^{\circ}$  C. Calibrations in 0.25 c.c. Time in seconds.

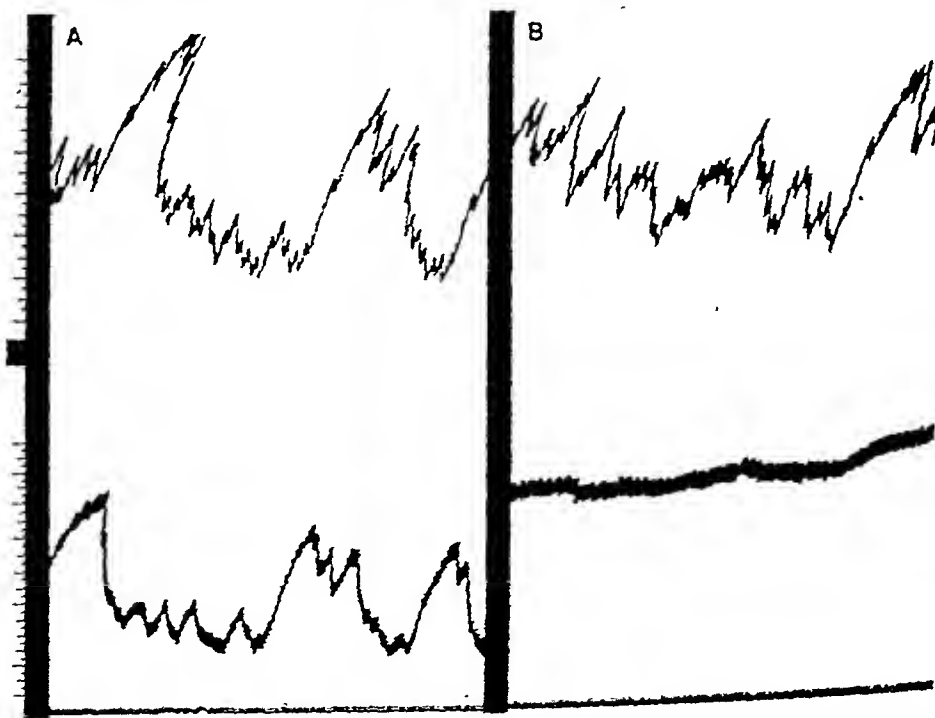


Fig. 4.—Volume changes recorded simultaneously in both hands of subject, K.K. A, Upper curve, right hand; lower curve, left hand. Synchronous variations present. B, Pressure of 70 mm. Hg at wrist of left hand. Upper curve, variations in right hand volume unchanged; lower curve, no variations in volume now observed in left hand. Bath temperature,  $32^{\circ}$  C. Room temperature,  $26^{\circ}$  C. Calibrations in 0.25 c.c. Time in seconds.

*D. The Effect of Raising Venous Pressure in the Hand.*—In eighteen subjects with marked or moderate variations in the volume of the hand,

raising the local venous pressure to 60 or 70 mm. Hg usually resulted in complete abolition of the spontaneous volume changes (Fig. 4B). In only a few cases did slight variations persist, but the changes in no way compared to those recorded previously. Simultaneous observations on the control hand showed that the spontaneous variations continued to occur (Fig. 4B).

## 2. Volume Changes in Other Parts of the Extremities.

The forearm, at a bath temperature of 32° C., was studied in thirty-nine subjects; thirty-four maintained a constant base line (Figs. 1B and 3A), and four showed slight, and one, moderate, variations. In those instances in which the arterial occlusion pressure at the wrist was removed, allowing the venous return from the hand to enter the forearm, variations synchronous with those observed in the hand, but of a lesser magnitude, usually became evident (Fig. 1A). The leg volume was found to be constant in eight of eleven subjects (Fig. 1B), while slight variations were observed in the remaining three. Only minor volume changes occurred in the feet of the four subjects who were examined.

## DISCUSSION

When the data presented are considered, it would seem that spontaneous limb volume changes are limited almost exclusively to the hand. The fact that some subjects who ordinarily showed no volume changes exhibited marked variations when they were asleep would be in favor of the view that these volume changes are truly spontaneous, and not the result of mental activity or of the action of sensory stimuli upon the tonus of blood vessels. This is further supported by the fact that the variations were abolished by a bath temperature of 45° C., under which conditions the blood vessels in the hand still respond to external stimuli.<sup>5</sup>

Since transient volume changes in an organ are essentially vascular in nature, the question arises as to what types of vessels are responsible for this phenomenon. With the exception of Burton,<sup>2</sup> who points out that there is possibly a venous component in the production of the spontaneous variations, the consensus seems to be that volume changes in an organ or an extremity are caused by alterations in arterial inflow. It is obvious, however, that these variations may also result from transient changes in the quantity of blood in the veins. That the venous bed\* can constrict independently of the arteries has recently been reported by Abramson and Ferris,<sup>5</sup> who found that both the hand and forearm respond to such stimuli as a pinch or mental arithmetic with a temporary diminution in limb volume. These changes were associated with a significant arterial constriction in the hand, whereas, in the forearm, either

\*"Venous bed" includes those vessels which cannot constrict against an internal pressure of 70 to 80 mm. Hg and do not materially contribute to the peripheral resistance. They include veins, venules, and capillaries.

no change was produced or an arterial dilatation occurred. From these data it was concluded that the volume changes in the hand, incident to a pinch or mental arithmetic, are the result of alterations in tone of both the arteriolar and venous beds, whereas, in the forearm, the response is almost entirely venous in nature. This view was supported by the observation that changes in forearm volume could no longer be elicited if the local venous pressure were first raised to 70 to 80 mm. Hg, under which conditions, according to Lewis,<sup>8</sup> the venules and capillaries in the skin are prevented from constricting. Therefore, our observation that spontaneous variations in the hand are eliminated by a similar procedure would be in favor of the assumption that these volume changes likewise result from alterations in venous tonus.

The objection might be raised that arterial inflow to the hand is materially interfered with by the presence of an artificially raised venous pressure. In order to test this possibility, we proceeded to ascertain the effect of the external application of different pressures at the wrist on blood flow to the hand. Since the usual procedure for the measurement of blood flow is inapplicable when venous pressure is high, it was necessary to resort to the following indirect means. Blood flow figures were first obtained on the forearm with no arterial occlusion pressure at the wrist, under which conditions the readings were the resultant of arterial inflow to the forearm and venous return from the hand, and the latter was directly proportional to the arterial inflow to the hand. Then, different pressures were applied and maintained at the wrist until the venous pressure in the hand reached a similar level and the outflow became equal to the inflow. By making blood flow measurements on the forearm under these conditions, information could be obtained as to whether or not there was any change in venous return from the hand, and, hence, in arterial inflow. Using this method, it was found that, in subjects with a normal or slightly elevated systemic blood pressure, external pressures varying from 40 to 60 mm. of Hg, which ordinarily reduce or completely abolish spontaneous variations, did not alter venous return from the hand, whereas a pressure of 70 mm. decreased it, but not significantly.

Occasionally, when both hands were utilized in order to study volume changes in one and blood flow in the other, it was noticed that spontaneous increases and decreases in arterial inflow were accompanied by rises and falls in the base line. This might suggest a causal relationship between the two phenomena. However, the observation that in other subjects variations in arterial blood flow were not accompanied by volume changes (Fig. 5) would tend to support the view that spontaneous changes in arterial inflow, of the magnitude generally observed in the hand, do not materially affect its volume. This is in accord with the observations of Holt and Lawson,<sup>4</sup> who found that

there could be significant changes in blood flow through the dog's hind leg with only slight variations in limb volume. These facts, however, do not rule out the possibility that a *significant* reduction in arterial inflow will decrease hand volume. For example, as has been stated before, Abramson and Ferris<sup>5</sup> found that with a strong, noxious stimulus, such as a pinch, a marked decrease in flow to the hand results, and, under these conditions, a diminution in hand volume may occur, even when the venous effect is eliminated by the application of a pressure of 70 to 80 mm. Hg to the wrist. Therefore, in the presence of marked spontaneous alterations in arterial inflow, an arterial factor may play a part in producing the changes in hand volume.

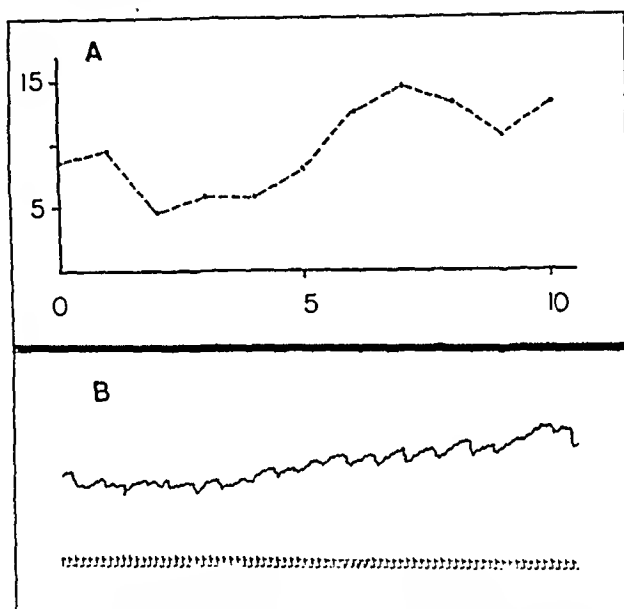


Fig. 5.—Blood flow measurements and volume changes in the hand of the same subject, L.A. A, Graph depicting spontaneous variations in blood flow, representative of changes present throughout experiment. Abscissa, minutes. Ordinate, blood flow in cubic centimeters per minute per 100 c.c. limb volume. B, Curve representative of volume changes present throughout experiment. Time in seconds. Bath temperature, 32° C. Room temperature, 26° C.

Capps<sup>10</sup> has shown that the veins of the hand possess tonus which is subject to temperature changes, i.e., cold constricts them and heat dilates them. In this connection it is of interest that, in the case of the hand, the base lines were of different types at bath temperatures of 19°, 32°, and 45° C. Fig. 2 reveals the transition from a constant volume at the low temperature to marked spontaneous variations at 32°, and the return to a steady base line at the high temperature. This would tend to indicate that, when veins are excessively constricted or dilated by external factors, no spontaneous alterations in caliber occur, and that the maximal variability in size is present when the skin temperature is normal.

From the foregoing, it would seem that, under physiologic conditions, the hand is intermittently changing in volume largely as a

result of alterations in the quantity of blood present in the veins, venules, and capillaries, and that the capacity of this venous bed is, in turn, dependent upon changes in venous tone.

#### SUMMARY AND CONCLUSIONS

1. By means of the plethysmographic method, spontaneous variations of limb volume were studied in forty-seven normal subjects, including persons of all ages between the second and eighth decades.

2. Spontaneous variations were found to be characteristic of the hand, and were absent or insignificant in the forearm, leg, and foot.

3. These variations occurred most frequently in young, normal adults and less often in persons of advanced age. They were marked during sleep and disappeared at high and low bath temperatures.

4. Raising the venous pressure to 60 or 70 mm. Hg, which prevents venous constriction without materially affecting arterial inflow, consistently caused the variations in the hand to disappear.

5. It is concluded that spontaneous variations in the volume of the hand are largely the result of alterations in the caliber of the venous bed, although an arterial component probably also plays a role.

6. The studies presented lend further support to the view that changes in the volume of an extremity do not necessarily reflect alterations in arterial inflow.

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## THE EFFECTS OF NITRITES AND XANTHINES ON CORONARY INFLOW AND BLOOD PRESSURE IN ANESTHETIZED DOGS

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**D**RUGS may be effective in improving myocardial blood supply by decreasing resistance to flow through normal channels or by dilating collaterals. The latter has been dealt with by several investigators.<sup>1-4</sup> This paper is concerned only with the former.

The empirical use of the nitrites began with the clinical observations of Brunton,<sup>5</sup> and, of the xanthines, with those of Babcock<sup>6</sup> and Ask-anazy.<sup>7</sup> The clinical trials were followed by many experimental investigations on the effect of these drugs on the heart and the coronary vessels. Such studies include observations on the inflow into the aorta or the coronary vessels, perfused under constant pressure,<sup>8-11, 40</sup> or on the outflow from the coronary sinus and/or pulmonary artery<sup>12-14, 44</sup> of perfused hearts (beating, quiescent, and fibrillating); on the changes in diameter of isolated arterial rings;<sup>10, 15</sup> on the coronary artery inflow under constant or declining pressure in heart-lung or whole animal preparations;<sup>3, 16</sup> on the coronary sinus outflow in heart-lung preparations or the whole animal;<sup>17-22</sup> and on the measurement of the inflow into the coronary arteries, perfused directly from the aorta, by means of the thermostromuhr.<sup>23-25</sup> The clinical, and, to some extent, the experimental aspects of this subject have been reviewed in several recent papers.<sup>26-28, 48</sup>

Despite the variety of methods, each with its own peculiar pitfalls, nearly all investigators agree that these drugs have a vasodilating action on the coronary vessels. The fact remains, however, that alterations in the coronary blood flow in the intact animal may differ significantly in extent and even in direction from what would be anticipated as a result of active changes in the size of the coronary vessels, because of varying degrees of extravascular compression by the contracting cardiac muscle,<sup>29, 31-35</sup> changing cardiac output (mechanical, reflex, and metabolic effects<sup>29, 30</sup>), and alterations of blood pressure per se.<sup>36</sup> These cannot be completely studied in the whole animal by measuring the inflow with the thermostromuhr or by measuring the outflow from the coronary sinus, for these yield only the mean flow; furthermore, the latter has been shown to be subject to serious error.<sup>31, 37, 38</sup>

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It therefore becomes of practical importance to study both the rate of inflow at any given moment, as well as the mean or total inflow into the coronary artery, and to take, simultaneously, an adequate record of the phasic variations of the aortic pressure, using preparations which correspond as nearly as possible to the intact animal. Such experiments have been made possible by the development by Gregg and Green<sup>39</sup> of a method for optically recording, at each instant in the heart cycle, the rate of inflow into a coronary artery, together with the aortic pressure. This paper deals with the application of their method to the study of changes in coronary flow produced by the nitrites and xanthines.

### METHOD

Thirteen dogs, weighing from 11 to 23 kg., were anesthetized with morphine (40 mg., given subcutaneously) and either sodium barbital (200 to 250 mg. per kilogram) or sodium pentobarbital (15 to 20 mg. per kilogram), given intravenously. Artificial respiration was started, and the heart was exposed by resection of the left fourth and fifth ribs and suspended in a pericardial cradle. The animal's blood was rendered noncoagulable by the intravenous administration of heparin (75 units per kg.), plus chlorazol fast pink (80 mg. per kg.) or calcomine fast pink 2BL\* (120 to 160 mg. per kg.). A cannula was then introduced either into the descending ramus of the

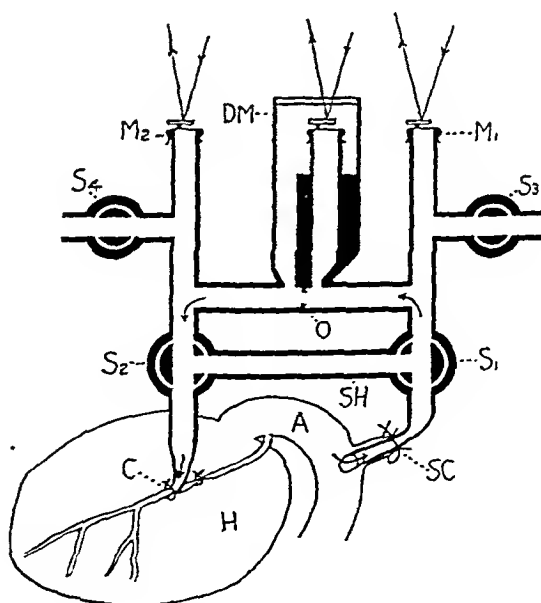


Fig. 1.—Schematic diagram of the apparatus used in measuring the coronary blood flow. A, Aorta; C, descending ramus of the left coronary artery; DM, differential manometer; H, heart; M<sub>1</sub> and M<sub>2</sub>, pressure manometers; O, orifice; S<sub>1</sub>, S<sub>2</sub>, S<sub>3</sub>, and S<sub>4</sub>, stopcocks; SC, subclavian artery; SH, shunt. When flow is being registered the stopcocks are turned so that blood flows from the cannula in the subclavian artery; SC, through the orifice, O, and thence into the coronary artery, C, as indicated by the arrows. The blood, in flowing through the orifice, causes the lateral pressures above and below the orifice to differ; that on the upstream side is the higher. This difference in pressure, which is proportional to the square of the rate of flow, is recorded by the differential manometer, DM, which is connected to the system immediately above and below the orifice. The pressure manometers serve to record the animal's blood pressure. When the flow meter (the orifice and differential manometer, taken together, constitute the flow meter) is being calibrated, the blood flowing from the aorta to the coronary artery is directed by the stopcocks S<sub>1</sub> and S<sub>2</sub> through the shunt, SH. The calibrating fluid is then directed into the flow meter through stopcock S<sub>3</sub>, and its rate of flow measured with a graduate as it flows out through stopcock S<sub>4</sub>. The arrows indicate the paths of the light beams used in recording the flow and pressures.

\*Courtesy of the Calco Chemical Company, Inc.

left coronary artery or one of its large proximal branches. This cannula was connected, through a flow meter, to a cannula inserted into the aorta by way of the left subclavian or carotid artery, so that the area to be studied was at all times perfused by a pulsatile stream of blood from the animal's own aorta (see Fig. 1). When a branch of the coronary artery was used, the main vessel proximal to the side branch was clamped while records of the coronary flow were being made.

Both intracoronary and intravenous injections were given. For the former, the drugs were dissolved in not more than 0.5 to 2.0 c.c. of Locke's solution, or a similar amount of blood previously withdrawn from the animal. The total dose was given by way of the coronary cannula over a period of approximately ten seconds. At this rate of injection, no significant alterations in the blood pressure in the coronary artery occur. For intravenous injections, larger doses, dissolved in 10 c.c. or more of Locke's solution, were used. Simultaneous records of aortic pressure and coronary flow were taken at frequent intervals prior to injection of the drug and until recovery had occurred. Most of the injections were intracoronary because the smaller dosage allowed more frequent injections.

The flow was recorded by means of the differential manometer and "minute-orifice" meter described by Gregg and Green,<sup>39</sup> with certain modifications.<sup>40, 41</sup> The differential manometer records the rate of flow by deflecting a light beam which is focused on a photokymograph. The meter is calibrated at frequent intervals during an experiment by running fluid through it at known rates of flow and simultaneously recording the deflection of the differential manometer beam. The aortic pressure was registered by a rubber-membrane optical manometer similar to that devised by Gregg.<sup>42</sup> The rate of flow (in cubic centimeters per minute) at any instant is ascertained by comparing the deflection of the differential manometer beam at that instant with the deflections obtained during the above-mentioned calibrations (Figs. 2 and 4). The total flow during any given period was ascertained by measuring the area on the record bounded by the flow curve, the zero flow line, and the ordinates demarcating the beginning and end of the interval. Since the deflection of the differential manometer beam is proportional to the square of the rate of flow, it is necessary, in order to compute the area correctly, to reconstruct the flow curve with a linear ordinate scale. This reconstruction was accomplished by means of the square root extractor devised by Green.<sup>43</sup> (See also Gregg and Green.<sup>39</sup>)

## RESULTS

*Normal Flow Curve.*—In order to understand the effects of drugs, it is necessary first to review the characteristics of a "normal" flow curve. Fig. 2A may be conveniently used for this purpose. The lowest line records the rate of flow (*FL*), upward movement indicating an increase. The upper lines (*AP* and *CP*) record the aortic pressure on the aortic and coronary sides of the meter. At the end of diastole the rate of flow is rapid, i.e., 53 c.c. per minute, but, with the onset of isometric contraction (1), the rate diminishes abruptly to 20 c.c. per minute as a result of the compressing effect exerted by the contracting cardiac muscle. The rate of flow increases during the rise of aortic pressure, but usually decreases slightly in the latter half of systole (see segments *B* and *C*). In this record the rate of flow at the peak of aortic pressure is 34 c.c. per minute, and, at the end of systole (2), 33 c.c. per minute. The rate of flow increases rapidly during isometric relaxation and then declines gradually during the latter part of diastole as aortic pressure falls.

*Nitrites.*—The effect of the intracoronary injection of 3 mg. of sodium nitrite is illustrated in segment *B* of Fig. 2. The rate of flow at the end of diastole (1) was 63 c.c. per minute; at the end of isometric contraction (minimal rate of systolic flow), 27.5 c.c. per minute; at the peak of aortic pressure, 52 c.c. per minute; and, at the end of systole (2), 48.5 c.c. per minute, despite a decline of aortic pressure from

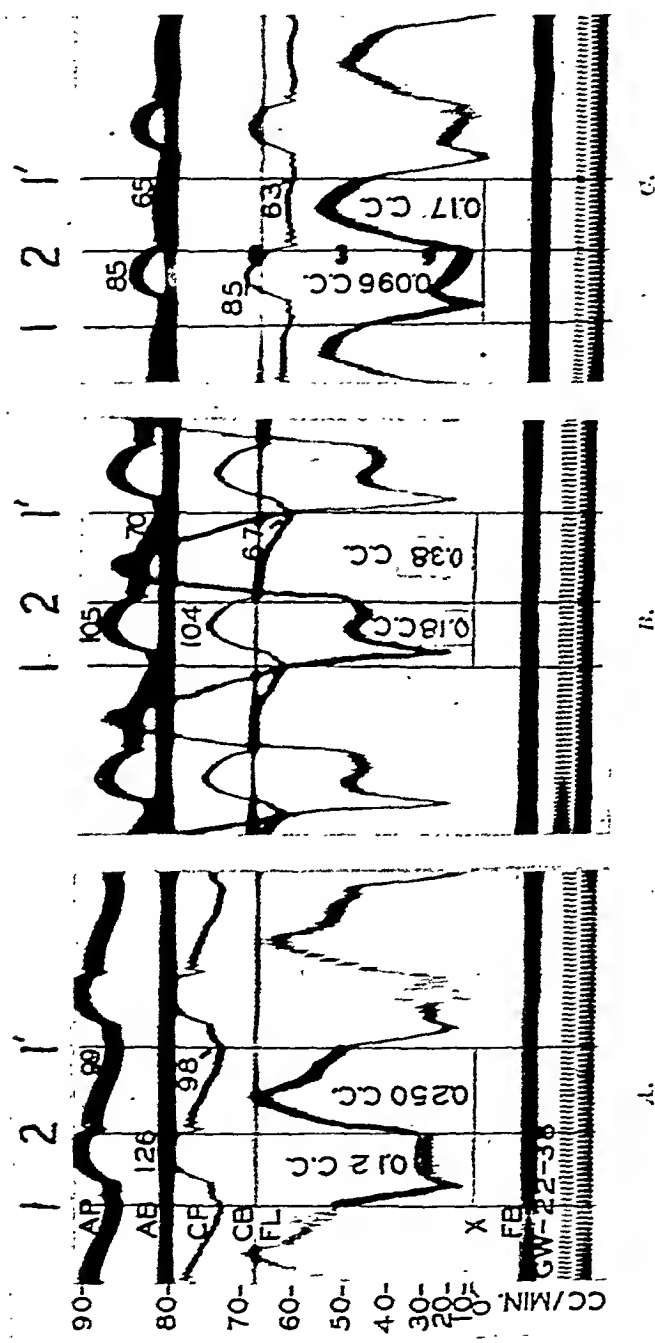


Fig. 2.—Segments of a record showing the effects on blood pressure and coronary flow of injecting 3 mg. of sodium nitrite into the coronary artery. The lowest curve, *FL*, which records the rate of flow at each instant, was made with the differential manometer, *D.M.*, *Fig. 1*. Upward movement indicates increased flow. The inked line *X* indicates the position which the upper edge of the flow line *FL* would occupy during zero flow. The rate of flow at any instant may be read from the scale at the left (read to top of the flow line). The two upper curves, *AP* and *CP*, were recorded by means of the two pressure manometers, *AM* and *CM*, respectively, of *Fig. 1*. The pressures, in millimeters of mercury, at the systolic peak and at the end of diastole are indicated by the figures accompanying the pressure records. Segment *A* was taken immediately before the injection of nitrite. Segment *B* was taken 40 seconds, and segment *C*, 7.7 minutes, after the injection of the drug. Time interval, 0.02 second.

126/98 in the control record to 104/67. After 7.7 minutes (segment *C*) the rates of flow had diminished to less than the control values, and the aortic pressure continued to fall.

The figures adjacent to the flow curve record the total flow for the portion of the heart cycle in which they are placed. For instance, in

segment *A* (Fig. 2) the flow during systole (1-2) was 0.12 c.c., and, during diastole (2-1'), 0.25 c.c., i.e., in this record, the systolic flow was 32 per cent of the cycle flow. Multiplying these figures by the heart rate (104 per minute) gives a total systolic flow of 12.5 c.c. per minute. Similarly, the flow during diastole was 26 c.c. per minute. For the cycle the total flow was therefore 38.5 c.c. per minute, which corresponds to the average rate of flow obtained by other methods. Thirty-five seconds after the injection of the nitrite (segment *B* of Fig. 2) the systolic flow had increased to 0.18 c.c., and the diastolic flow to 0.38 c.c. Although the average deflection of the flow curve in diastole in segment *B* appears to be almost twice that in segment *A*, the total flow increased only from 0.25 to 0.38 c.c. This is because the deflection of the flow meter beam was nonlinear. (See calibration at the left of the figure.) Because of the increased rate of flow and the increased heart rate, the total systolic flow increased to 19.5 c.c. per minute, the diastolic to 41.5 c.c. per minute, and the total (or average) cycle flow to 61 c.c. per minute.

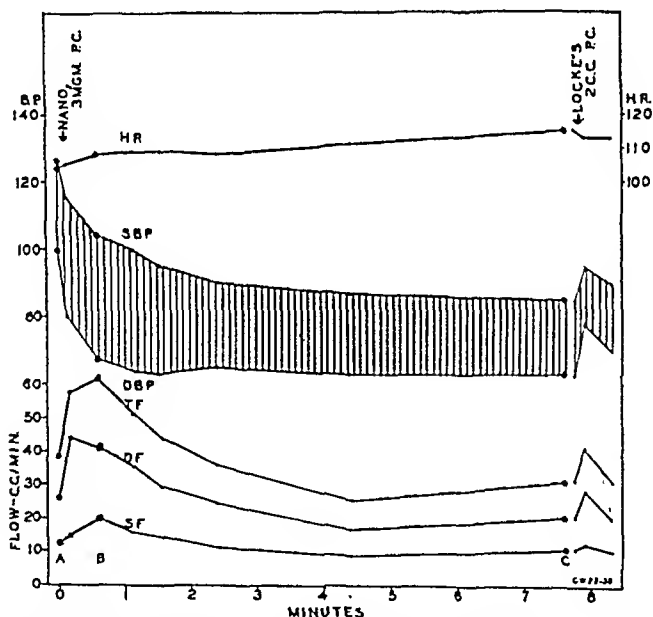


Fig. 3.—Plot of heart rate (*HR*), systolic (*SBP*) and diastolic (*DBP*) blood pressure, total systolic flow per minute (*SF*), total diastolic flow per minute (*DF*), and total cycle flow per minute, *TF* (*SF* + *DF*). Upper scale at left (*BP*) indicates blood pressure in millimeters of mercury. Lower scale at left indicates total flow in cubic centimeters for one minute for all three lines (*SF*, *DF*, and *TF*). Scale at right (*HR*) is heart rate in cycles per minute. Encircled points *A*, *B*, and *C* are from the similarly labeled segments of Fig. 2.

In order to illustrate the successive changes in rate of flow that occurred in this experiment, the data from the control and the seven records which were taken at intervals after the injection of the nitrite are presented in a plot in Fig. 3. The encircled points, labeled *A*, *B*, and *C*, correspond respectively to the similarly labeled segments of Fig. 2. The immediate increase in the flow persisted for 1.5 minutes, when probably because of the decline of aortic pressure, it decreased below

the control value and only very gradually returned toward normal. Early in the course of this work it became apparent that the intracoronary injection of a small quantity of Locke's solution, and, fre-

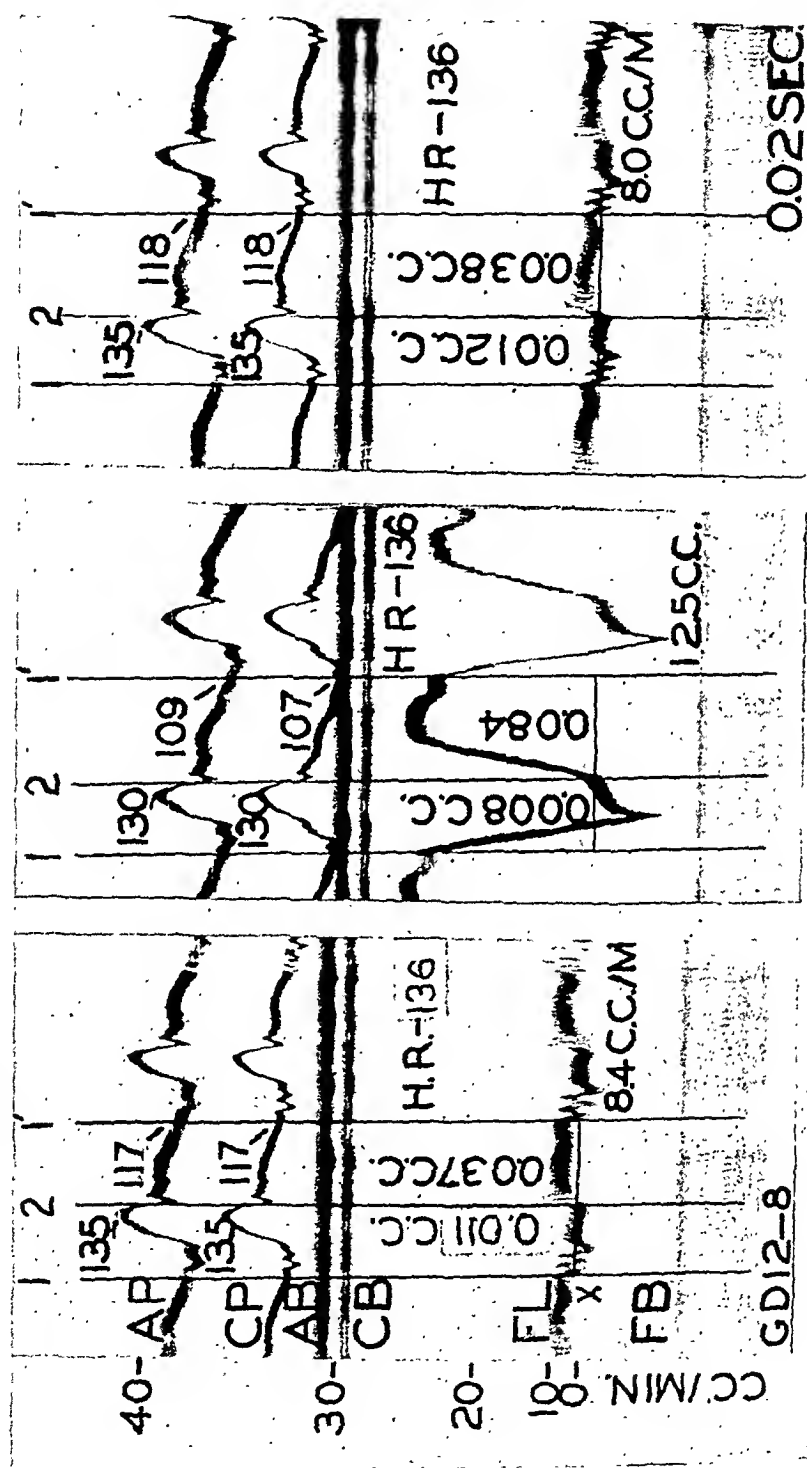


Fig. 4.—Segments of a record illustrating the effects of an intracoronary injection of 5 mg. of theophylline (mono-ethanolamine). A, Control; B, twenty seconds after injection; and C, 5.8 minutes after injection. See Fig. 2 for explanation of lettering.

quently, even of blood, resulted in a momentary increase in coronary flow, and it therefore became necessary to control the effect of an intracoronary injection of a drug by the intracoronary injection of a similar quantity of blood or Locke's solution without the drug. The brief effect of 2 c.c. of Locke's solution is shown at the right of Fig. 3.

*Xanthines.*—As a result of the intracoronary injection of 5 mg. of theamine (Fig. 4, segment *B*) the rate of coronary flow at the end of diastole (1) increased from 8.5 to 24.5 c.c. per minute. The minimal rate of systolic flow (at the end of isometric contraction) changed from -5 to -14 c.c. per minute, that at the peak of aortic pressure from 4 to -4 c.c. per minute, and that at the end of systole (2) from 2.5 to 4 c.c. per minute. Thus, despite the elevated rate of inflow during diastole (1), the rate diminished to a value below zero, so that the drug<sup>\*</sup> actually caused a considerable backflow during most of the ejection phase of systole (1-2).

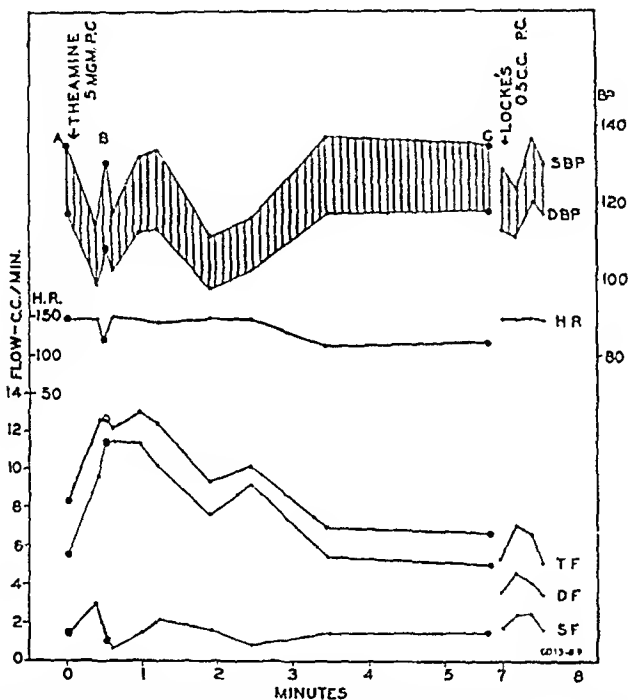


Fig. 5.—Plot of all of the data obtained after an injection of theamine. The encircled points are for the similarly labeled segments of Fig. 4. See Fig. 3 for explanation of lettering.

Fig. 5 is a plot of all of the effects of the drug injection just described. The marked oscillations of the blood pressure cannot be ascribed to the drug, for they were present throughout the experiment, and are probably Traube-Hering waves. The flow during the entire heart cycle and during diastole was increased and remained elevated for about 2.5 minutes, when it declined to values slightly below those of the control record.

*Tabulation of Data.*—In order to obtain an estimate of the changes in the average rate of flow, but more particularly to allow a statistical analysis of the mechanisms of the action of the drugs, based on their effects on the intramural flow, we measured and tabulated the rates of flow at the four critical points in the heart cycle described above for

\*For curves illustrating the effects of intravenous injections of the nitrites and xanthines, see Green.<sup>45</sup>

TABLE

NO.	DRUG	R. A.	DOSE (MG.)	DOG WT.	DOG NO.	REC. NO.	H.R.		S/C		E/C	
							B	A	B	A	B	A
1	No	C	5	13.5	GD. 14	7	158	160	0.35	0.36	0.21	0.21
2	No	V	50	13.5	GD. 14	9	158	154	0.40	0.43	0.20	0.21
3	Ng	C	2	11.4	GW. 9	27	114	118	0.45	0.44	0.36	0.31
4	Ng	V	10	11.4	GW. 9	28	112	122	0.46	0.41	0.32	0.32
5	No	V	100	11.4	GW. 9	29	114	117	0.45	0.35	0.33	0.32
6	No	V	100	23	GW. 12	9	90	100	0.36	0.36	0.27	0.30
7	Ng	C	0.6	23	GW. 12	12	74	82	0.32	0.31	0.27	0.30
8	No	V	100	13	GW. 14	1	212	212	0.45	0.45	0.29	0.34
9	No	V	30	13	GW. 14	2	212	212	0.48	0.48	0.30	0.31
10	No	C	30	13	GW. 14	4	212	212	0.46	0.46	0.27	0.25
11	No	C	30	10.5	GW. 20	20	150	158	0.50	0.50	0.45	0.45
12	No	C	30	10.5	GW. 20	21	154	160	0.50	0.50	0.30	0.38
13	Ng	C	0.3	10.5	GW. 20	22	150	150	0.50	0.50	0.40	0.40
14	Ng	C	1.2	12.5	GW. 22	29	142	146	0.50	0.48	0.36	0.38
15	No	C	20	12.5	GW. 22	33	141	143	0.47	0.47	0.31	0.33
16	No	C	30	12.5	GW. 22	38	104	106	0.45	0.43	0.31	0.32
17	Ng	C	1.2	12.5	GW. 22	40	116	118	0.45	0.45		
18	No	C	30	19	GW. 23	12	86	88	0.37	0.32	0.30	0.28
19	Ng	C	1.2	19	GW. 23	14	71	75	0.38	0.37	0.28	0.30
20	Ng	C	2.4	19	GW. 23	16	76	80	0.36	0.33	0.28	0.27
21	Am	C	5	11.5	GD. 10	2	148	154	0.42	0.43	0.28	0.28
22	Am	C	20	11.5	GD. 10	7	150	150	0.40	0.40	0.28	0.30
23	Am	V	20	11.5	GD. 10	8	133	133	0.35	0.35	0.30	0.32
24	Am	C	0.9	23	GD. 11	12	135	140	0.48	0.47	0.32	0.32
25	Am	C	1.8	23	GD. 11	15	139	146	0.49	0.46	0.31	0.26
26	Am	C	9	23	GD. 11	16	150	152	0.51	0.46	0.30	0.28
27	Am	V	48	23	GD. 11	19	150	162	0.45	0.44	0.27	0.27
28	Th	C	20	15.5	GD. 12	4	146	154	0.44	0.44	0.27	0.26
29	Th	V	20	15.5	GD. 12	7	137	146	0.41	0.40	0.25	0.24
30	Th	C	5	15.5	GD. 12	8	136	136	0.41	0.41		
31	Th	V	40	15.5	GD. 12	10	139	170	0.37	0.40	0.20	0.21
32	Am	C	5	15.5	GD. 12	13	138	136	0.39	0.39	0.25	0.23
33	Am	V	45	15.5	GD. 12	16	150	167	0.37	0.38	0.26	0.23
34	Am	C	5	15.5	GD. 12	18	145	145	0.40	0.40	0.26	0.24
35	Th	C	2.5	15.5	GD. 12	19	140	140	0.39	0.39	0.22	0.26
36	Am	V	50	15.5	GD. 12	20	148	156	0.41	0.41	0.24	0.23
37	Th	C	5	13.5	GD. 14	1	158	158	0.40	0.41	0.24	0.24
38	Th	C	5	13.5	GD. 14	3	162	161	0.40	0.39	0.27	0.24
39	Th	V	50	13.5	GD. 14	5	162	168	0.38	0.41	0.20	0.25
40	Am	C	1	15.5	GJ. 5	2	191	193	0.42	0.34	0.26	0.28
41	Am	C	1	15.5	GJ. 5	4	184	186	0.42	0.37	0.27	0.24
42	Th	C	1	20.5	GD. 17	3	140	153	0.45	0.43		
43	Th	C	4	20.5	GD. 17	4	140	140	0.48	0.43		

Table of data obtained after all experimentally satisfactory injections of the drugs. NO<sub>2</sub>, Sodium nitrite; NG, nitroglycerine; AM, aminophyllin\*; TH, theanin†; R.A., route of administration; C, injected into coronary artery; V, injected intravenously; Dose, in milligrams; Dog Wt., in kilograms; Rec. No., serial number of the record; H.R., heart rate in beats per minute; S/C, systole cycle ratio; E/C, ejection cycle ratio; B.P., blood pressure in millimeters of mercury; B, before giving the drug; A, after giving the drug; S, systolic blood pressure measured at the peak of the aortic pressure curve; P, pressure at the onset of protodiastole; D, diastolic pressure measured at the

\*Theophylline-ethylenediamine, courtesy G. D. Searle & Co.

†Theophylline mono-ethanolamine, courtesy Eli Lilly Co.

all injections included in this series of experiments. The data (Table I) are from a control record and a record showing approximately the maximum effect of the drug, omitting consideration of the first ten to fifteen seconds after intracoronary injections in order to avoid the immediate effects of the injection. Two of the above critical points,

I

B. P.						FLOW							
B			A			I		P. S.		E. S.		E. D.	
S	P	D	S	P	D	B	A	B	A	B	A	B	A
84	83	62	74	73	50	0.0	6.0	11.5	10.0	0.0	0.0	16.5	21.0
132	130	113	94	93	80	5.0	2.0	9.0	10.0	9.0	10.0	12.5	17.5
94	82	69	82	73	58	-10.5	-9.0	17.5	20.5	10.0	9.0	35.5	37.0
95	88	70	100	86	64	5.0	5.0	37.0	30.5	32.5	23.5	52.0	58.0
96	84	60	82	70	45	0.0	20.5	37.0	42.0	28.0	27.0	51.5	55.0
105	80	60	88	64	45	10.0	20.5	20.5	31.0	18.5	10.0	47.0	52.0
97	90	67	89	80	51	9.0	14.5	22.5	24.0	11.0	9.0	44.0	46.0
124	122	92	86	80	55	-13.5	-12.0	17.0	23.5	0.0	0.0	29.0	35.0
120	115	96	117	110	90	-10.0	-10.0	23.5	23.5	0.0	0.0	35.0	32.5
122	105	98	112	98	90	0.0	12.0	20.0	31.5	0.0	22.5	29.0	53.0
114	94	68	105	86	59	20.5	21.0	31.5	32.5	20.5	21.0	44.5	46.0
104	83	62	95	79	54	27.0	23.5	32.5	34.0	20.0	16.5	46.0	44.0
94	78	58	90	67	55	25.5	29.0	27.5	29.0	16.0	16.0	46.5	46.5
95	80	60	92	76	42	0.0	28.5	20.0	38.0	20.0	37.0	38.5	48.0
95	82	60	89	73	48	16.0	30.0	26.5	36.5	15.0	24.5	45.0	54.0
126	126	98	104	95	67	20.0	27.5	33.5	51.0	33.0	48.5	53.0	63.0
88	85	65	84	70	53	11.0	22.0			24.0	34.5	47.5	60.0
140	135	90	140	136	95	30.0	18.0	28.0	27.0	36.0	31.0	42.0	40.0
123	117	75	116	107	70	25.0	22.0	34.5	31.0	34.0	31.0	30.0	35.0
119	110	68	118	109	64	10.0	10.0	31.0	30.0	30.0	30.0	31.0	30.0
130	125	103	125	122	100	-15.0	-15.0	17.0	19.0	12.0	12.0	28.0	28.0
82	80	55	75	65	41	-16.0	-12.0	8.5	10.0	8.0	8.0	31.0	29.0
70	68	42	90	82	42	-8.0	-15.0	16.0	20.0	8.0	8.0	27.0	32.5
96	90	67	100	96	70	8.0	8.0	22.0	23.5	17.5	22.0	33.5	42.0
95	90	70	96	93	69	8.0	12.0	19.5	20.5	13.0	25.0	30.0	42.0
92	88	66	97	94	68	10.0	0.0	21.5	29.5	17.0	30.0	31.0	51.0
94	90	70	92	89	63	8.0	13.0	25.5	31.5	22.0	25.0	34.0	41.5
126	122	110	127	122	107	-2.5	-15.0	3.0	5.5	2.5	6.5	6.0	22.5
109	107	92	113	110	95	0.0	0.0	4.5	4.5	2.5	3.5	5.5	8.5
135	132	117	130	126	107	-5.0	-14.0	4.0	-4.0	2.5	4.0	8.5	24.5
106	104	90	111	109	96	0.0	0.0	3.5	2.0	2.5	0.0	5.0	7.0
101	98	81	100	96	80	-2.5	-6.5	4.5	0.0	2.0	0.0	6.5	14.0
110	102	90	107	90	76	-3.5	0.0	5.0	3.5	3.0	2.5	7.0	9.5
95	91	77	102	97	83	-4.0	-7.0	3.0	3.5	0.0	3.5	7.0	10.0
98	94	82	101	98	81	-3.0	-6.0	4.0	0.0	2.0	0.0	6.0	9.5
99	96	81	95	90	79	-3.0	-5.0	5.0	4.0	2.5	2.5	6.5	8.5
100	98	82	100	97	80	0.0	0.0	7.5	8.0	5.0	5.0	12.5	13.5
96	92	77	98	94	68	-2.0	-4.0	9.0	10.5	4.0	5.5	14.0	25.0
100	98	80	92	87	65	1.5	2.0	9.0	4.0	2.5	4.0	12.5	18.0
116	112	99	115	115	95	-12.0	-33.0	11.0	5.0	16.0	15.0	20.5	41.5
130	124	103	125	118	95	-2.5	-16.0	12.5	8.0	13.5	12.0	30.0	38.0
85	82	64	80	77	60	15.5	13.0	26.0	19.0	17.5	15.5	39.0	44.0
72	69	58	73	71	60	12.5	0.0	25.5	19.0	18.0	25.0	38.0	43.5

onset of isometric contraction; Flow, coronary rate of flow in cubic centimeters per minute; I, minimal rate of flow at approximately the end of isometric contraction; P.S., rate of flow at peak of aortic pressure; E.S., rate of flow at end of systole; E.D., rate of flow at end of diastole. The G.W. animals were anesthetized with sodium barbital, the G.D. animals with sodium pentobarbital. These two series of animals were also used for other drug injections (see Green, Boyer, Wehrin, and Kent).<sup>4</sup>

i.e., the end of systole, corresponding to the peak of the peripheral coronary pressure curve,<sup>32</sup> and the end of diastole, are those at which, according to Gregg and Green,<sup>30</sup> the rate of change of volume elastic and myocardial compression forces are minimal under normal conditions. The rate of inflow at these points in the cycle, therefore, most nearly represents intramural flow. We can, accordingly, use changes in the rate of inflow at the end of diastole as an index of the degree of



contraction or relaxation of the coronary vessels, and there is relatively little danger that this index will be affected by extravascular compression. Similarly, changes in the rate of inflow in the latter part of systole may be regarded as reflecting variations of myocardial compression, plus changes in the caliber of the coronary vessels. Under the action of certain drugs, however, the peak of the peripheral coronary pressure curve is advanced from the end of systole to approximately the peak of the aortic pressure curve.<sup>48</sup> Therefore the resistance to flow may actually be increased during most of systole as a result of the action of the drug, but it may be decreased at the very end of systole. Such a change in the form of the resistance curve occurs rather regularly with epinephrine,<sup>41</sup> and was observed in two experiments with the xanthines in which the peripheral coronary pressure was measured. In order to evaluate this possible change in dynamics, we have measured the flow at the third critical point, namely, the peak of the aortic pressure curve. The fourth critical point which we have measured and tabulated in order to give a further idea of the extent of the reduction in flow caused by extravascular compression is the inflow at the end of isometric contraction (minimal systolic flow).

*Comparison of Nitrites and Xanthines.*—The data from Table I are summarized in Tables II and III. Injections which, either because of the smallness of the dose or nonreactivity of the animal, resulted in no appreciable change in flow or blood pressure have been eliminated. The difference between the nitrite and xanthine experiments with respect to the average control pulse pressure and heart rate may be ascribed to a difference in anesthetics or to slight differences in the operative technique which was used in the two groups of experiments.

The effects of the drugs have been expressed as the average of the per cent change. Mean blood pressure, calculated as the arithmetical mean of the systolic and diastolic blood pressures, tended to be lowered by the nitrites. This effect was greater the larger the dose, and was, therefore, more marked with the larger intravenous injections. The xanthines had, in general, no significant effect on mean blood pressure. The larger doses of the latter group of drugs, particularly the intravenous injections, increased the pulse pressure moderately and the heart rate slightly more than did the nitrites. Both intracoronary and intravenous injections of the nitrites tended to decrease the systole-cycle ratio and to increase the ejection-cycle ratio slightly, whereas the intracoronary injections of the xanthines tended slightly to decrease both ratios, but, because of the variability of the effects, as shown by the magnitudes of the sigma values, these small differences are perhaps not significant.

In order to separate the changes in peripheral coronary resistance from the effect of blood pressure variations caused by the drugs, we

TABLE II

		NIT. COR.	NANT. COR.	NIT. VEIN	NANT. VEIN
No. Exp.		10	14	5	7
M.B.P.	Av. Control	86.5	91	91.7	88.1
	Av. % change	-11.7	-1.1	-22.1	-1.2
	$\sigma$ (%)	8	6.5	15	8
P.P.	Av. Control	31	20.9	31.4	20.4
	Av. % change	+11.8	+12	+1.3	+29
	$\sigma$ (%)	16	21	19	31
H.R.	Av. Control	136.5	149	137	153
	Av. % change	-2.8	+1.5	+2.8	+5.9
	$\sigma$ (%)	2.2	3	4	8
S/C	Av. Control	0.445	0.435	0.425	0.391
	Av. % change	-1.3	-1.6	-5.6	+2
	$\sigma$ (%)	2.2	5.7	10.5	3.6
E/C	Av. Control	0.316	0.273	0.282	0.246
	Av. % change	+2.2	-4	+6.4	+0.4
	$\sigma$ (%)	3.2	14.5	7.1	19
D.I.	Av. Control	0.563	0.308	0.560	0.222
	Av. % change	+50	+82	+63	+45
	$\sigma$ (%)	28	76	32	19
E.S.I.	Av. Control	0.151	0.106	0.200	0.069
	Av. % change	+38	+19	+2	+2
	$\sigma$ (%)	43	68	32	46
P.S.I.	Av. Control	0.226	0.140	0.236	0.167
	Av. % change	+37	-9	+17	-15
	$\sigma$ (%)	26	25	42	23
E.S.C.	Av. Control	0.412	0.209	0.360	0.152
	Av. % change	+39	+120	+98	+62
	$\sigma$ (%)	18	150	38	18
P.S.C.	Av. Control	0.337	0.180	0.324	0.115
	Av. % change	+56	+163	+89	+132
	$\sigma$ (%)	37	151	50	60

Summary of data from Table I. Nit. Cor., averages of results of injection of sodium nitrite and nitroglycerine into the coronary artery; Nit. Vein, same for injections into jugular vein; Nant. Cor., averages of results of injection of theamine and aminophyllin into the coronary artery; Nant. Vein, same for injections into jugular vein; No. Exp., number of records in each of above groups included in ascertaining the average; M.B.P., mean blood pressure; P.P., pulse pressure (aortic systolic pressure, minus aortic diastolic pressure); H.R., heart rate (beats per minute); S/C, systole-cycle ratio; E/C, ejection-cycle ratio; D.I., diastolic flow index; E.S.I., flow index at end of systole; P.S.I., flow index at peak of aortic systolic pressure; (all indices calculated as flow, in cubic centimeters per minute, divided by pressure, in millimeters of mercury; E.S.C., difference between diastolic index and index at end of systole; P.S.C., difference between diastolic index and index at peak of aortic pressure; Av. Control, average of the control values; Av. % change, average of the individual percentage change calculated as:

$$\frac{\text{reading before giving drug} - \text{control reading}}{\text{control reading}} \times 100$$

$\sigma$  (%) = square root of sum of the squares of the differences between the average percentage change and the individual percentage changes, divided by the number of observations (see Rider,<sup>20</sup> p. 88). Note: Margin numbers 9, 13, 18, 19, 20, 30, and 37 of Table I were omitted in preparing this table.

have calculated an index of flow, i.e., the ratio of the rate of flow in cubic centimeters per minute to the simultaneously existing aortic pressure in millimeters of mercury. Such ratios have been calculated for the peak of aortic systolic pressure (P.S.I.), for the end of systole (E.S.I.), and for the end of diastole (D.I.). The significance of these

ratios depends, of course, upon whether or not the flow shows a linear correlation with pressure. We believe that it is reasonable to assume that it does, over the range of pressure change which occurred. Assuming that at the end of diastole the vascular bed was not being affected by active myocardial extravascular compression, the percentage change in the diastolic index (D.I.) will indicate the effect of the drug on the coronary vessels which control blood flow, i.e., an increase in the ratio, expressed as + per cent, indicates active vasodilatation, and vice versa. It is apparent from Table II that both groups of drugs and both routes of administration increased the D.I. and that, furthermore, the magnitude of the effect was, on the average, comparable among the four groups.

It may be assumed that, if no other factors intervened, the percentage changes in the indices at the peak of aortic systolic pressure (P.S.I.) and at the end of systole (E.S.I.) would be the same as for the diastolic index (D.I.). It is apparent from Table II that the increase in both systolic indices was, in general, less than that in the diastolic indices for both groups of drugs and both routes of administration. The failure of the E.S.I. to increase in proportion to the D.I. was most noticeable when the two groups of drugs were given intravenously, but was also readily apparent after intracoronary injection of the xanthines. The difference between the effect of the xanthines and nitrites on the P.S.I. was striking; on the average, the index was decreased as a result of giving the former, whether intravenously or into the coronary artery, whereas the nitrites increased the P.S.I. almost as much as the D.I.

These results on the indices suggest that the intracoronary and intravenous injection of the xanthines and the intravenous injection of the nitrites produce a dual effect. One is a decrease in peripheral resistance throughout the cycle, caused by dilatation of the vessels which control coronary flow, and the other is an increase in the resistance to flow during systole, brought about by an increase in the extravascular compression exerted by the contracting myocardium. To view this latter effect in another way, we have subtracted the index at the peak of aortic pressure (P.S.I.) and that at the end of systole (E.S.I.) from the diastolic index (D.I.) in each record. These differences (P.S.C. and E.S.C., respectively) represent the extent of the reduction of the vascular bed caused by systole. The percentages of increase in these differences which were caused by the drugs are tabulated in Table II. The extent of the reduction of the vascular bed at the end of systole (E.S.C.), as calculated by this method, was, on the average, one and a half times as large after intravenous injection of the xanthines and almost three times as large after intracoronary injection of the xanthines as that caused by intracoronary injection of the nitrites. The reduction caused by intravenous injection of the nitrites was of the order of twice that caused by intracoronary injection of nitrites. The

reduction of the extent of the vascular bed at the peak of the aortic pressure (P.S.C.) caused by the xanthines was, on the average, two to three times that brought about by the nitrites.

TABLE III

DRUG	TOTAL FLOW C.C./MIN.				TOTAL FLOW % BY M.B.P.		
	ROUTE	BEFORE	AFTER	CHANGE %	BEFORE	AFTER	CHANGE %
Nitrite	C	28.6	34.5	20.0	0.33	0.45	36.5
Xanthine	C	16.7	24.0	44.0	0.18	0.27	46.0
Nitrite	V	20.8	22.8	9.6	0.22	0.31	45.0
Xanthine	V	10.9	13.1	20.0	0.12	0.15	22.5

Average change in total flow per minute and average change in total flow per minute per millimeters of mercury, calculated from data given in Table I. Nitrite includes sodium nitrite and nitroglycerine; Xanthine includes theamine and aminophyllin; C, injected into coronary artery; V, injected into jugular vein; Before, average control value; After, average value at the instant of the maximum effect of the drug; % change =  $\frac{\text{after} - \text{before}}{\text{before}} \times 100$ .

It has been our experience that a fairly close approximation to the total (or average) flow per minute is obtained by adding the product of the rate of flow at the end of diastole times the diastole-cycle ratio to the product of the rate of flow at the end of systole times the systole-cycle ratio. The averages of the data on the total flow per minute calculated in this way, and on the percentage change of the total flow produced by the drugs (for the same experiments that are analyzed in Table II) are presented in Table III. The xanthines apparently caused a greater increase than the nitrites, by both routes of administration, but the increase in terms of actual cubic centimeters was not very large for the intravenous injections of either group of drugs. When, however, as in the right half of the table, the decline of aortic pressure is taken into account, the effects of the two groups of drugs are more nearly comparable.

#### DISCUSSION

The interest of the therapist in this subject will lie in the question whether these drugs are capable of producing a favorable relationship between the work of the heart and the coronary blood flow. Although the cardiac output was not directly measured in these experiments, the behavior of the mean blood pressure and pulse pressure makes it seem likely that the nitrites materially decrease the work of the heart, whereas the xanthines have no such action, or may even increase the work. Furthermore, it has been pointed out in the description of the data on these experiments that the xanthines appear to exert a stimulant action on the myocardium. Under such circumstances it may not be justifiable to attribute vasodilatation solely to the action of the drug, for the increased vigor of contraction may, in itself, by virtue of increased liberation of metabolites, be in part responsible for the vasodilatation. The latter mechanism of increasing coronary blood flow may be considered ineffective from the point of view of enhancing coronary reserve.

Starr, et al.,<sup>45</sup> found evidence that theophylline increased cardiac output without increasing the size of the heart; they interpreted this to indicate increased vigor of contraction or "tone." They also found that the xanthines increased cardiac work without significantly changing the heart rate and with but slight elevation of the blood pressure, whereas the nitrites tended slightly to decrease both the cardiac work and blood pressure. The available information suggests, then, that the actions of these drugs are similar in the anesthetized dog and in man.

#### SUMMARY AND CONCLUSIONS

The effect of intra-coronary and intravenous injection of nitrites and xanthines on the flow of blood from the aorta into a coronary artery was studied in anesthetized dogs by means of a new type of optically recording flow meter.

These two groups of drugs increase the diastolic coronary flow, both absolutely and relative to the aortic head of pressure; this demonstrates dilatation of the vessels which control coronary flow. With intra-coronary injection, the xanthines appear at times to exert a stimulant influence on the myocardium. With intravenous injection of both groups of drugs, the increased flow is caused more by augmentation of flow in diastole than in systole. In the case of the xanthines this is probably in part the result of the myocardial stimulant action. With both, changes in the dynamics of the circulation probably play a part; the net effect is an increase in the extravascular compression force exerted by the contracting myocardium.

Changes in cardiac output and systemic peripheral resistance, particularly after administration of the xanthines, complicated the observations so that it is not possible to state definitely whether the increase in flow was in all cases effective in increasing the nutrition beyond what was required by changes in the external work performed by the heart. The nitrites, on the other hand, tended to increase coronary flow at the same time that they decreased the blood pressure and cardiac work.

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THE RELATIONSHIPS OF LEAD I, CHEST LEADS FROM THE  
C<sub>3</sub>, C<sub>4</sub>, and C<sub>5</sub> POSITIONS, AND CERTAIN LEADS MADE FROM  
EACH SHOULDER REGION: THE BEARING OF THESE  
OBSERVATIONS UPON THE EINTHOVEN EQUILATERAL  
TRIANGLE HYPOTHESIS AND UPON THE  
FORMATION OF LEAD I

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SINCE our first demonstration of the diagnostic value of chest leads in acute myocardial infarction,<sup>1</sup> we have been interested in the relations between the limb and chest leads. As long as we used only one anterior chest position (the apex), these relations seemed capricious. Some patients with a normal precordial lead showed abnormalities in Lead I, whereas many with a normal Lead I had abnormalities in the precordial lead. However, when we began to take chest leads from the C<sub>3</sub>, C<sub>4</sub>, and C<sub>5</sub> positions and studied the relations of these multiple chest leads to Lead I, it quickly became apparent that the relationships were not so capricious as at first they had seemed to be. When CF<sub>3</sub> was abnormal and CF<sub>5</sub> normal, Lead I was usually normal. However, when CF<sub>5</sub> was abnormal, Lead I tended to be abnormal. Moreover, Lead I tended to resemble Lead CF<sub>5</sub> except for the fact that its deflections were likely to be smaller. A and B in Fig. 1 are examples of electrocardiograms which show the lack of correlation between abnormalities in Leads I and CF<sub>3</sub> and the rather striking correlation often observed between abnormalities in Leads I and CF<sub>5</sub>. Although this correlation is far from perfect, it is too close to be a coincidence.

After we had studied the relationships between Leads I and CF<sub>5</sub> in a number of cases, it occurred to us that CR<sub>5</sub> might show an even better correlation with Lead I than did CF<sub>5</sub>, because one variable would be eliminated, namely, the position of the right arm electrode. When Leads I and CF<sub>5</sub> were taken, this electrode was placed on the right arm for one lead and on the left leg for the other (two points which differ in potential) and this difference was recorded in Lead II; whereas, when Leads I and CR<sub>5</sub> were taken this electrode was placed on the right arm in both cases. When this point was tested, our supposition was borne out (Fig. 1C). There was a much closer correlation between the abnormalities in Leads I and CR<sub>5</sub> than between those in Leads I and CF<sub>5</sub>. There were still some exceptions which will be discussed below.

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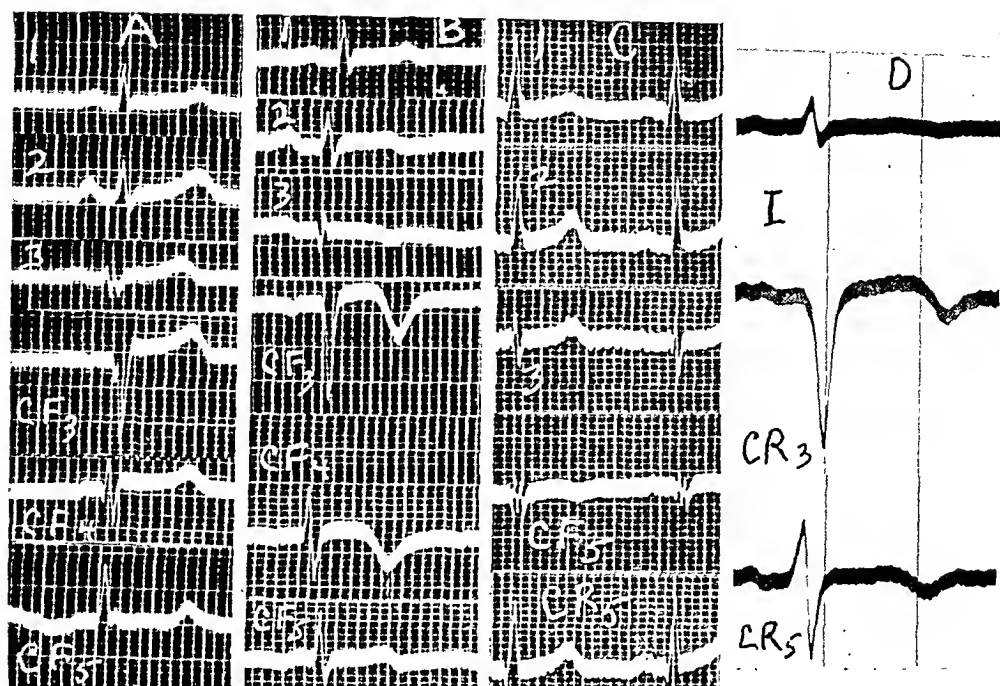


Fig. 1.—A, Similarity between contour of ventricular complexes in Leads I and  $CF_1$ . No resemblance between the QRS complexes of Leads I and  $CF_2$ . B, Same patient after a second attack of acute coronary occlusion. The similarity of contour in Leads I and  $CF_1$  persists; both have developed a slightly diphasic T wave. There is no resemblance, either of QRS complexes or T waves, between Leads I and  $CF_2$ . The QRS complex of Lead  $CF_1$  is somewhat like that of  $CF_2$  and Lead I, but the T wave, which resembles that of  $CF_1$ , is totally unlike those of Leads I and  $CF_2$ . C, In this case  $CF_1$  is unlike Lead I, whereas  $CR_1$  resembles Lead I (See text for explanation). D, The ventricular complexes of Leads I and  $CR_1$  are similar, although the deflections in  $CR_1$  are much larger. There is no resemblance between the QRS complexes of Leads I and  $CR_2$  (film speed, 75 mm. per second).

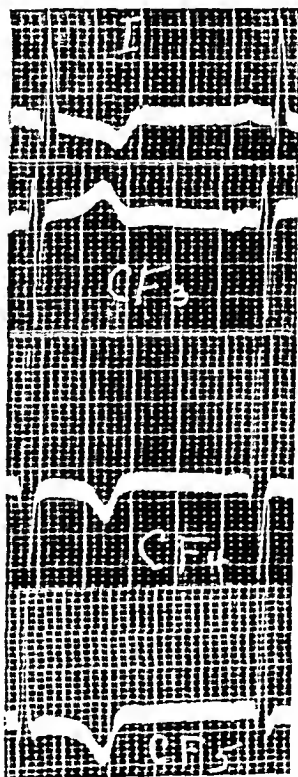


Fig. 2.—Leads I,  $CF_1$ ,  $CF_2$ , and  $CF_3$ . This is the pattern of chest leads in which the ventricular complexes of Leads I and  $CF_1$  may show some resemblance. It may occur when  $CF_2$  follows the pattern of  $CF_1$  more closely than that of  $CF_3$ .

As in the case of  $CF_3$ , no correlation was observed between abnormal patterns of Leads I and  $CR_3$  (Fig. 1D). As far as the  $C_4$  position was concerned, an abnormality which appeared at  $C_4$  and  $C_3$ , but not at  $C_5$ , did not tend to be reflected in Lead I (Fig. 1B). However, when an abnormality at  $C_4$  was associated with an abnormal pattern at  $C_5$ , Lead I also tended to be abnormal (Fig. 2). This is the explanation for the seemingly capricious relationship between leads from the apex or the  $C_4$  position and Lead I.

The close correlation between Leads I and  $CR_5$ , and the lack of correlation between Leads I and  $CR_3$  seemed to indicate that Lead I was being affected by the electrical activity of one part of the ventricular muscle much more than by the rest of this structure. In searching for an explanation of these relationships two possibilities occurred to us: (a) If the Einthoven equilateral triangle hypothesis were even approximately correct, it would mean that some electrical change was being picked up at the  $C_5$  position which influenced Lead I by affecting the potential in both arms and that an electrical change was being registered through the  $C_3$  position which did not produce a discoverable effect on Lead I because it did not materially change the potential in either arm. (b) The Einthoven hypothesis may not account fully for the phenomena which are observed; a certain portion of the ventricle which registers its effects at the  $C_5$  position may be causing a predominant change in potential in one arm without necessarily producing such changes in potential in the other extremities, as would be required by the Einthoven hypothesis. Probably no one would question the physical principles on which the Einthoven equilateral triangle hypothesis is based, but some of the assumptions which underlie its applicability to the human body are open to serious question. It is not necessary here to recapitulate the arguments pro and con, except to mention the work of Eyster, Maresch, and Krasno,<sup>2</sup> and Katz and Korey,<sup>3</sup> who have pointed out that there are marked differences in the conductivity of various body tissues. Their observations throw doubt upon the validity of the fundamentally important assumption of Einthoven that body tissues function as a homogeneous fluid conductor.

In order to investigate the above two possibilities, we attempted to devise a method of studying potential changes separately in the right arm and left arm. The method of Wilson, Johnston, Macleod, and Barker<sup>4</sup> for recording what they regard as the potential of a single area on the body could not be used, because it assumes the complete validity of the Einthoven equilateral triangle hypothesis, i.e., the hypothesis which we are attempting to test.

Many different procedures were employed, but, in most of them, the guiding principle was the study of the differences in potential which developed along lines extending more or less radially from the heart. It was thought that if electrodes could be placed along such a line, the changes in potential should take the same direction under all of them,

but that they might be greatest under the one nearest the heart. If such proved to be the case, one would be in a position to discover the directions of the potential changes in the extremities, even if deviations from the resting potential could not be measured quantitatively by such a procedure.

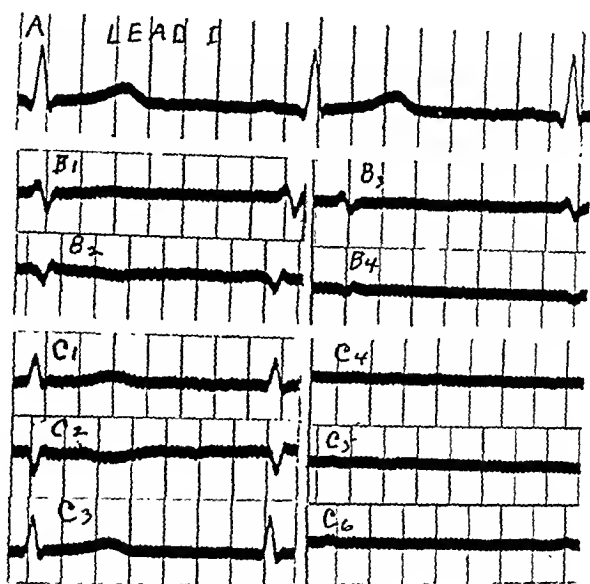


Fig. 3.—Various leads from a normal subject. The special leads in this and all other figures are designated so that positivity of the area mentioned first is represented by an upward deflection. A, Lead I. B<sub>1</sub> and B<sub>2</sub>: Leads from front and back of chest, respectively (about 2 inches from left arm), paired with the left forearm. B<sub>3</sub> and B<sub>4</sub>: Similar leads on the right side. C<sub>1</sub>: A lead from as high as possible in the left axilla, paired with the left forearm. C<sub>2</sub>: A lead from the top of the left acromial process, paired with the left forearm. C<sub>3</sub>: A lead on the right side, made in the same way as C<sub>1</sub>. C<sub>4</sub>: A lead on the right side, made in the same way as C<sub>2</sub>. C<sub>5</sub>: A lead from high in the left axilla to the tip of the left acromial process. C<sub>6</sub>: A similar lead on the right side. All these leads on the left side show far larger ventricular deflections than those on the right side. B<sub>2</sub> and B<sub>1</sub> are almost inverted images of B<sub>1</sub> and B<sub>3</sub>, respectively. The same is true of C<sub>1</sub> and C<sub>2</sub>. Note the similarity in contour (except for size of deflections) among C<sub>1</sub> (left axilla to left forearm), C<sub>3</sub> (left axilla to left shoulder), and Lead I.

Considerable difficulty was encountered in the practical application of such a method. It quickly became apparent that marked differences existed between the electrical fields of the right and left upper parts of the body; only small differences in potential tended to develop between adjacent areas on the right side, whereas there were often very large differences in potential between comparably situated areas on the left side (Fig. 3). Moreover, it was noted that, if one electrode were placed on an arm and the other on the front of the chest near the root of the arm, a tracing was obtained in which the deflections were likely to be opposite in direction from those which were registered when the electrode on the front of the chest was moved to a comparable point on the back (Fig. 3, B<sub>1</sub> and B<sub>2</sub>, B<sub>3</sub> and B<sub>4</sub>). It was obvious that both of these patterns could not represent the direction of the potential changes in the arm.

Among the earlier leads employed was one in which the left arm electrode was placed as high as possible in the axilla, between the arm and its attachment to the body, and the right arm electrode was placed

on the forearm of the same side. The ventricular deflections recorded on the right side were often so small as to be unrecognizable (Fig. 3,  $C_4$ ), but on the left they were sometimes almost half as large as those of Lead I (Fig. 3,  $C_1$ ). The thing which excited our interest was the fact that the general pattern of such a lead on the left side was likely to resemble that of Lead I. We then studied the tracing obtained on the left side by keeping the right arm electrode on the forearm and moving the left arm electrode directly across the root of the arm to the top of the acromion. In such a tracing the deflections were opposite in direction from those of the axilla-arm lead, and usually a little smaller (Fig. 3, compare  $C_1$  and  $C_2$ ).

It seemed from these observations that a lead made across the attachment of the arm from the axilla (left arm electrode) to the top of the shoulder (right arm electrode) should be nearly twice as large as one made from the left axilla to the left forearm, and that it should still retain its resemblance to Lead I (Fig. 3,  $C_3$ ). This proved to be the case. An extensive study was then made of these axilla-shoulder leads in both upper extremities. The most important facts which developed as a result of these studies were the following:

1. The ventricular complexes in the left shoulder electrocardiogram are usually astonishingly large, considering the fact that the electrodes are paired across the attachment of the arm, whereas those in the right shoulder electrocardiogram are very small (Fig. 3,  $C_3$  and  $C_6$ ). There are certain exceptions to these general rules: (a) patients with left ventricular hypertrophy or hypertension may have fairly large deflections in the right shoulder lead (Fig. 4,  $A_1$  and  $E_3$ ). However, they are nearly always smaller than those in the left shoulder lead, for these also tend to be larger than normal.\* (b) Patients with bundle branch block often have large deflections in the right shoulder lead; some are even larger than those from the left side (Fig. 4  $B_1$  and  $B_2$ ). (c) Persons with long chests and vertically placed hearts may show minimal deflections in the left shoulder lead; they are sometimes little, if any, larger than those obtained from the right shoulder lead (Fig. 4,  $C_1$  and  $C_2$ ). (d) Patients with anterior infarction may show extremely small QRS deflections in leads from the left shoulder region (Fig. 4,  $D_2$ ).

2. When electrodes are applied in the manner described above, the ventricular complexes obtained in leads from the left side look very much like those of Lead I (Fig. 3, Lead I and  $C_3$ ; Fig. 4,  $A_2$  and  $A_3$ ,  $E_1$  and  $E_2$ ); whereas those obtained in leads from the right side usually bear no resemblance to Lead I. The principal exceptions, which are likely to fail to show a resemblance between Lead I and the left shoulder lead, are the last three named in the preceding paragraph (Fig. 4  $B$ ,  $C$ , and  $D$ ).

\*The electrical activity of the left shoulder region in certain cases of hypertension is so great that ventricular deflections of considerable size may be recorded across the left arm 2 inches from the shoulder (Fig. 4,  $E_3$ ).

3. The average size of the auricular deflections is about the same in the right and left shoulder electrocardiograms. Sometimes they are larger on the right, and sometimes on the left (Fig. 5).

These observations are difficult to account for on the basis of Einthoven's equilateral triangle hypothesis. If, as he suggested, the

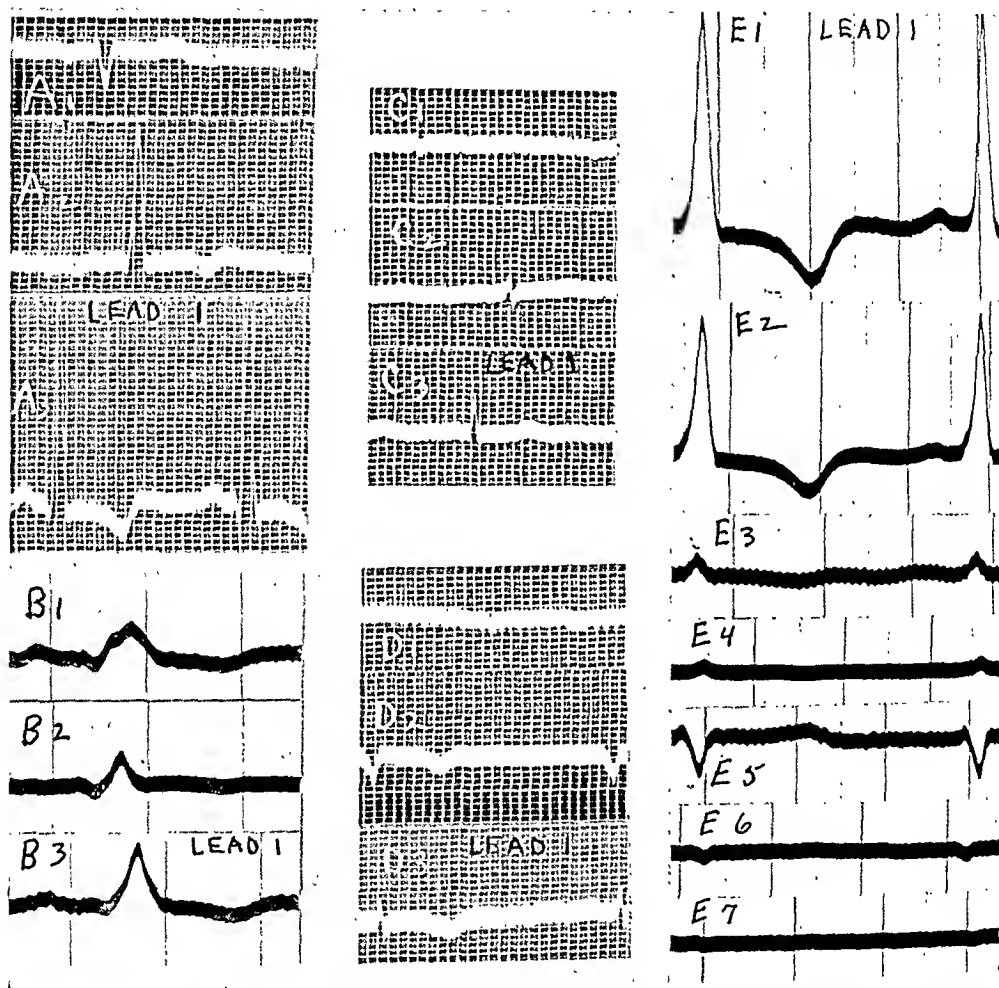


Fig. 4.—A, Patient with hypertension. A<sub>1</sub>: Lead from right axilla to right shoulder. A<sub>2</sub>: Lead from left axilla to left shoulder. A considerable difference of potential may develop across the root of the right arm in cases of hypertension, but, as in this case, much larger deflections are usually recorded across the root of the left arm. The ventricular complexes in the lead from the left side resemble those of Lead I (A<sub>1</sub>). B, Patient with left bundle branch block. B<sub>1</sub>: Right shoulder-axilla lead. B<sub>2</sub>: Left axilla-shoulder lead. B<sub>3</sub>: Lead I. In cases of bundle branch block the electrical activity about the right shoulder may be as great as or greater than that on the left side. Under these circumstances the contour of the tracing in the lead across the left arm often fails to resemble closely that of Lead I (Film speed, 75 mm. per second). C, Patient with long chest and vertically placed heart. C<sub>1</sub>: Right shoulder-axilla lead. C<sub>2</sub>: Left axilla-shoulder lead. C<sub>3</sub>: Lead I. The electrical activity about the left shoulder is little greater than that on the right side. Compare C<sub>2</sub> with A<sub>2</sub> and E<sub>2</sub>, all of which were made with the electrodes in similar positions. D, Patient with healed anterior infarction. D<sub>1</sub>: Right axilla-shoulder lead. D<sub>2</sub>: Left axilla-shoulder lead. D<sub>3</sub>: Lead I. The QRS complex in the lead across the root of the left arm is represented solely by a small negative deflection. This does not dominate the QRS wave of Lead I, although the T waves are similar in the two leads. E, Patient with hypertension and left ventricular hypertrophy. E<sub>1</sub> is Lead I. E<sub>2</sub> is a left axilla-shoulder lead. E<sub>3</sub> is a lead made with the electrodes paired across the left arm from the inner to the outer side, 2 inches from the shoulder. E<sub>4</sub>: Electrodes paired across the left arm, halfway between the shoulder and the elbow. E<sub>5</sub> is a right axilla-shoulder lead. E<sub>6</sub>: Lead across right arm, 2 inches below the shoulder. Note that the differences in potential across the left upper arm are greater than those on the right side and are comparable to those recorded in the axilla-shoulder leads. In one case of hypertension and left ventricular hypertrophy, recognizable deflections were obtained in a lead made across the left forearm.

heart is far enough from the arms to function as an electrical point in relation to them, neither shoulder electrocardiogram should be of any size, for in each shoulder lead both electrodes are on one side of the heart and are situated more or less on a line extending radially from it. Einthoven's concept does not account for the large size of the ventricular deflections in the left shoulder electrocardiogram, which are sometimes as large as those in Lead I, nor does it explain the resemblance of the left shoulder electrocardiogram to Lead I, which is striking in most subjects except for a few with anterior infarction, ventricular hypertrophy, bundle branch block, or vertically placed hearts. Finally, although the ventricular potentials in the right shoulder region behave in accordance with the Einthoven hypothesis, except in the case of bundle branch block and ventricular hypertrophy, the auricular potentials do not, for they are larger than would be expected.

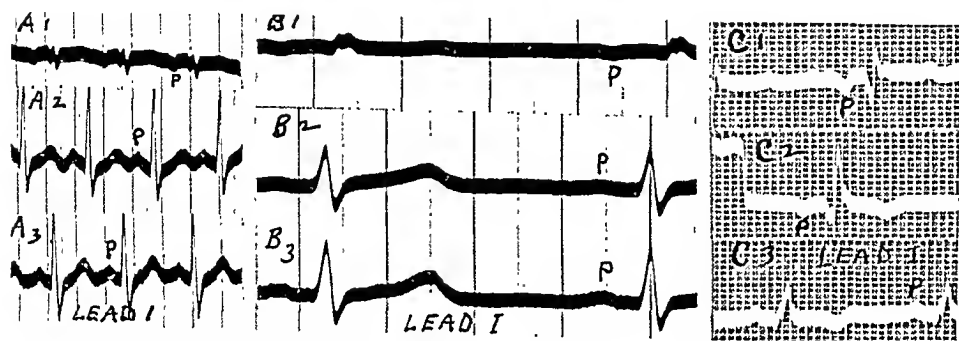


Fig. 5.—Examples of types of auricular deflections in leads made across the attachments of the arms. *A*, Patient with posterior type of infarction. *A*<sub>1</sub>: Right shoulder-axilla lead. *A*<sub>2</sub>: Left axilla-shoulder lead. *A*<sub>3</sub>: Lead I. Although, in comparison with Lead I, the P wave in the lead across the root of the right arm is much less reduced in size than the QRS complex, it is smaller than the P wave in a lead on the left side. Had the polarity been the same on the right as on the left, the P wave would have been upright (Film speed, 25 mm. per second). *B*, Normal subject. *B*<sub>1</sub> and *B*<sub>2</sub> were made in the same way as *A*<sub>1</sub> and *A*<sub>2</sub>, respectively. The P wave in the leads from the right and left sides are about equal in size, in spite of the disparity in the ventricular deflections (Film speed, 75 mm. per second). *C*, Patient with hypertension and anterior type of infarction. *C*<sub>1</sub>: Right axilla-shoulder lead. *C*<sub>2</sub>: Left axilla-shoulder lead. *C*<sub>3</sub>: Lead I. In this case the P wave in the lead from the right side is larger than in that from the left. The QRS complex in the right-sided lead is larger than usual as is often the case in hypertension.

We had reason to hope that further experimentation might lead to an explanation of the correlation we have observed between Leads I and CF<sub>5</sub>, so we took tracings with electrodes in various other positions. First, we made an attempt to "fractionate" Lead I. One lead was taken from the right forearm (right arm electrode) to the suprasternal notch (left arm electrode), and a second from the suprasternal notch (right arm electrode) to the left forearm (left arm electrode). The former gave a very small deflection, whereas the latter gave a much larger one which greatly resembled Lead I (Fig. 6A). Second, in order to obtain further information concerning the correlation between Lead I and tracings from the C<sub>5</sub> position, leads from the suprasternal notch (right arm electrode) to the left supraclavicular space, left shoulder, left arm, and left axilla were compared with a lead from the suprasternal notch to

the  $C_5$  position (Fig. 6C). These leads were quite similar; the deflections grew larger as the left arm electrode approached the  $C_5$  position.\* Moreover, all resembled Lead I. Third, it was found that a lead from

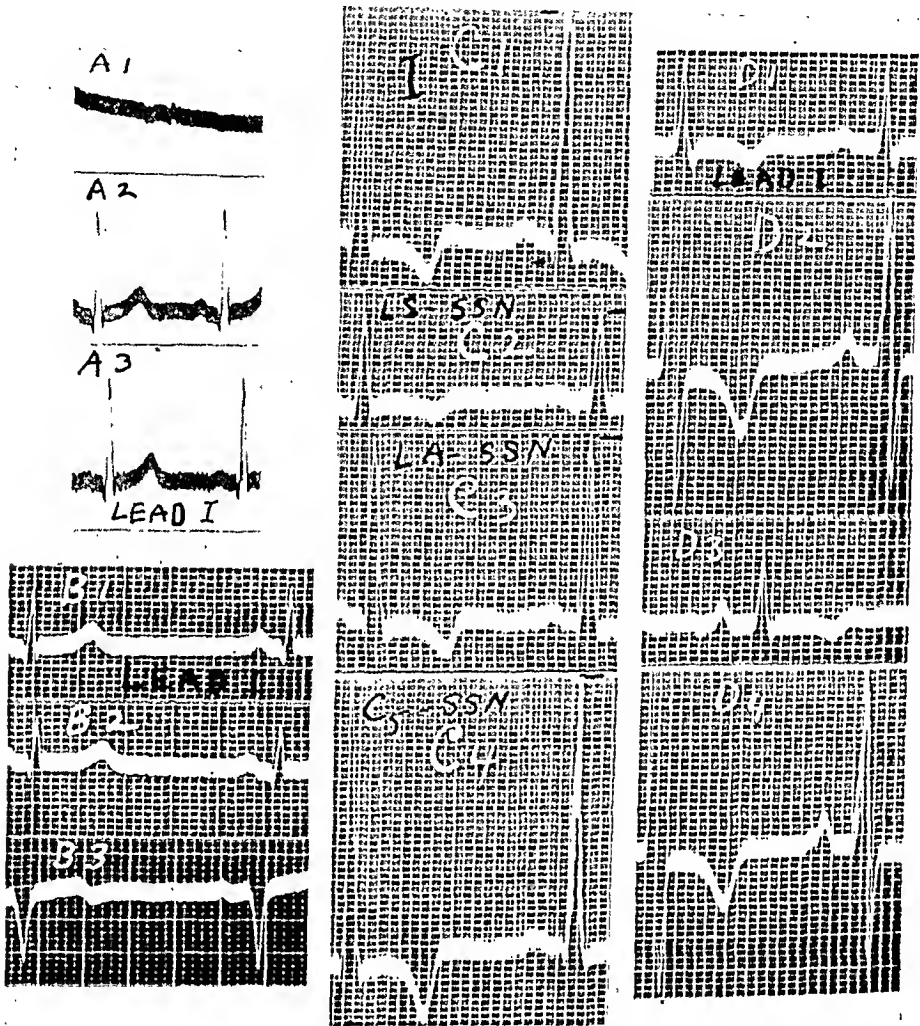


Fig. 6.—A, Normal subject. A<sub>1</sub> is a lead from the suprasternal notch to the right arm. A<sub>2</sub>: From the left arm to the suprasternal notch. A<sub>3</sub> is Lead I. Note the small ventricular deflections in the lead from the right side, the large deflections in that from the left side, and the resemblance of the latter to Lead I. The P waves in the lead from the right side are reduced comparatively much less than the QRS complexes. B, Patient with anterior type of infarction. B<sub>1</sub> is Lead I. B<sub>2</sub>: A lead from the left arm to the suprasternal notch. B<sub>3</sub> is CR<sub>3</sub>. Note that the ventricular deflections in the lead from the left arm to the suprasternal notch, as well as in Lead I, bear no resemblance to CR<sub>3</sub>. C, Patient with hypertension. C<sub>1</sub> is Lead I. C<sub>2</sub>, C<sub>3</sub>, and C<sub>4</sub> are leads made from the top of the left shoulder, the left arm, and the C<sub>5</sub> position, respectively, to the suprasternal notch. Note the similarity of the ventricular complexes in all of these leads. D, Patient with aortic insufficiency and left ventricular hypertrophy. D<sub>1</sub> is Lead I. D<sub>2</sub> is CR<sub>3</sub>. D<sub>3</sub> is a lead from the left arm to the suprasternal notch. D<sub>4</sub>: A lead from the C<sub>5</sub> position to the suprasternal notch. D<sub>1</sub> and D<sub>3</sub>, as well as D<sub>2</sub> and D<sub>4</sub>, are practically identical. The leads which include the left arm (D<sub>1</sub> and D<sub>3</sub>) resemble those which include the C<sub>5</sub> position (D<sub>2</sub> and D<sub>4</sub>), except for the comparatively larger S waves in the tracings from the C<sub>5</sub> position.

the suprasternal notch to the left shoulder did not reflect an abnormality which was present in a lead from the suprasternal notch to the C<sub>5</sub> posi-

\*The correlation between leads from the suprasternal notch to the left arm and to the C<sub>5</sub> position is as close as that between Leads I and CR<sub>3</sub> (Fig. 6D).



tion, provided that this abnormality was absent in a lead from the suprasternal notch to the  $C_s$  position (Fig. 6B).

These observations suggest that (1) some one and the same part of the ventricular muscle influences predominantly the changes in potential in the left shoulder and in the  $C_s$  position and does not influence materially those in the right arm, (2) the auricles influence the potential change in both arms to about the same degree, and (3) the part of the ventricular muscle whose electrical activity is reflected at the  $C_s$  position has no significant effect upon the potential changes in either arm (slight effects which it may have will be discussed below).

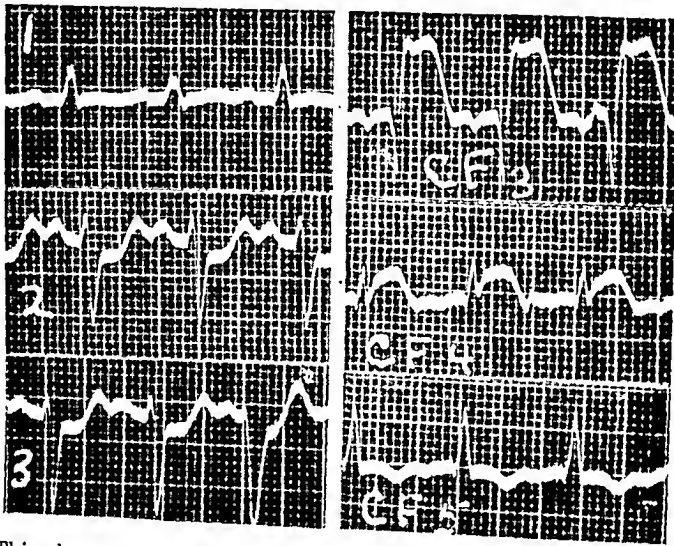


Fig. 7.—This electrocardiogram was obtained from a woman, 68 years old, five days after the onset of a succession of attacks of severe epigastric pain. At the time the tracing was made she was critically ill; death occurred a few hours later. Note the marked RS-T segment deflection in  $CF_3$ , and its absence in Leads I and  $CF_6$ . At necropsy, a fresh infarct, infiltrated with blood, was found; it involved the anterior third of the interventricular septum and extended to the anterior surface of the heart. On the surface the lesion was approximately 1 cm. wide and 4.5 cm. long; its long diameter paralleled the anterior part of the interventricular groove. Microscopic examination showed that the lesion did not seem to have extended into the anterior wall of either ventricle much beyond the limits described above for the grossly visible infarction. The anterior descending branch of the left coronary artery was completely obstructed 1 cm. beyond its origin. An additional finding was a small healed infarct at the extreme apex.

We do not possess adequate data, which should be based on careful electrocardiographic study and subsequent necropsy localization of the lesion, to state with certainty where these two portions of the ventricular muscle are situated. Such information as we do possess would suggest that, when infarction is reflected in  $CR_3$  and not in chest leads made to the left of the  $C_s$  position, the lesion is likely to lie in or near the anterior part of the interventricular septum (Fig. 7). On the other hand, when the lesion is reflected best in the  $C_s$  position and in Lead I, it is likely to be located farther to the left. It may be found on further observation that the part of the ventricular muscle which affects the left arm and the  $C_s$  position is the anterolateral portion of the left ventricle; whereas the part which affects the  $C_s$  position and not the  $C_s$  position



or the arms is situated close to the anterior portion of the interventricular groove. This would not be unexpected if one considered the relative positions of  $C_3$  and  $C_5$  on the chest wall.

One other observation might be mentioned in this connection. In cases of healed posterior infarction, when Leads I and  $CR_5$  are normal, a lead from the left axilla to the left shoulder has a normal contour and tends to resemble Leads I and  $CR_5$ , although the deflections are smaller (Fig. 8). Thus, the electrical activity of the posterior wall of the left ventricle is probably not reflected to any extent in the left shoulder region or in the  $C_5$  position.

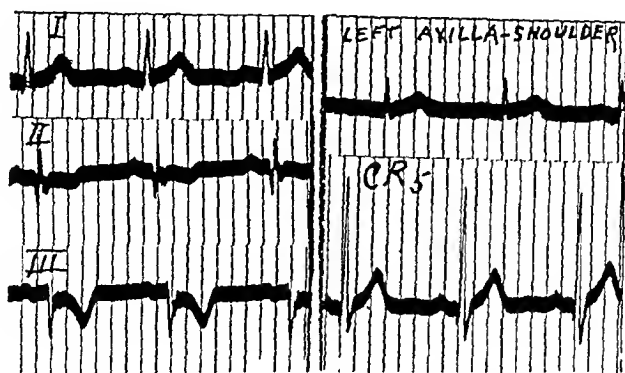


Fig. 8.—Electrocardiogram of patient with healed infarction involving the posterior wall of the left ventricle. Note the resemblance of the lead made with electrodes placed in the left axilla and on the tip of the left acromial process to Leads I and  $CR_5$ . The leads from the left shoulder region in cases of posterior infarction are likely to resemble those obtained from normal subjects.

These observations suggest that the ventricular complex of Lead I is not formed in accordance with Einthoven's conception. Rather, it seems as if its form is determined largely by the electrical activity of the left arm. This extremity seems to function as a poor sort of chest lead and to be dominated by a part of the ventricular muscle. It appears that a certain portion of the left ventricle is too close (electrically) to the root of the left arm (except in persons with long chests and vertically placed hearts) to allow the heart to function as Einthoven conceived that it would (i.e., as an electrical point) with regard to this extremity.

It is our belief that the occasional cases in which there is no correlation between Leads I and  $CR_5$  (except for some patients with bundle branch block, vertical hearts, and anterior infarction) can be accounted for in two ways: (1) there are individual variations in the size of the heart and conformation of the chest, so that comparable areas of the heart's electrical field are not tapped from the  $C_5$  position in each subject, and (2) certain areas adjacent to that part of the ventricular muscle which is tapped at the  $C_5$  position probably influence the potential in the left arm to some extent.

We are aware that small deflections in the right shoulder leads, as we have taken them, do not necessarily mean that potential changes in the right shoulder are insignificant. This is the type of electrical ac-

tivity that one would expect to find if Einthoven's assumption that the heart functions as an electrical point were correct. It may be that the right arm is usually far enough away from the ventricles to satisfy this assumption. There is little doubt that the right arm plays some part in the formation of Lead I. In so far as the P wave is concerned, it is just as important as the left arm. Occasionally in cases of left ventricular hypertrophy, and usually in cases of bundle branch block, the right arm plays an important role in the formation of the ventricular complex of Lead I. Certain observations made with a two-beam galvanometer\* (to be reported later) suggest that the small  $Q_1$  in normal subjects is often derived from the right side. Moreover, other ventricular deflections may be modified by the effect of the right arm. However, as a rule, the influence of the right arm on Lead I is not great enough to blur the resemblance of the main QRS and T deflections in Lead I to those obtained from the left shoulder region.

Although the right arm may play a greater part in the formation of Lead I than is shown by our leads from the right shoulder region, this would not invalidate the tentative conclusions we have drawn from our experiments. The similarity of contour between Lead I, tracings obtained from the  $C_3$  position, and leads from any two points along a line from the suprasternal notch leftward to the arm and thence downward to the  $C_5$  position is such that we have been unable to account for it by any explanation except the one we have proposed.

We do not mean to imply from the above observations that the taking of limb lead electrocardiograms is not as useful a procedure as it ever was. However, unless or until evidence can be produced to support the assumptions, now under question, which Einthoven had to make to construct the equilateral triangle hypothesis, such procedures as vector analysis and attempts to measure the potential changes of a single area by Wilson's method appear to be of dubious value. We should regard limb leads as empirical; they are not yet subject to the mathematical magic of the equilateral triangle.

From the standpoint of practical clinical electrocardiography, it must be remembered that the anterior infarcts which do not produce abnormalities in Lead I are more likely to cause abnormalities in leads from the  $C_3$  position than from  $C_5$ . Therefore, if only one chest lead is to be taken (a procedure which seems unwise at the moment), the precordial electrode should be placed medial to the apex impulse rather than lateral to it; there are a few patients who will show a Q-wave, an RS-T segment deviation, or a T-wave inversion in  $CF_3$ , and not in other leads. However, it must not be forgotten that leads from the  $C_3$  position will occasionally show a Q wave in normal controls, and we suspect that T-wave inversion in this lead is occasionally of no pathologic significance. Hence, the abnormalities which appear in this lead must be interpreted with circumspection.

\*Loaned through the courtesy of the Sanborn Instrument Company.

## SUMMARY

1. The ventricular complexes of Lead I and of chest leads from the  $C_5$  position resemble one another, both when they are normal and when they are abnormal, except for the fact that those of Lead I are usually smaller. Lead  $CR_5$  shows a closer correlation with Lead I than does Lead  $CF_5$ . There is no correlation between Lead I and chest leads from the  $C_3$  position. Abnormalities in the contour of tracings made from the  $C_4$  position tend to have a counterpart in Lead I only when they are also recordable from the  $C_5$  position.

2. When electrocardiograms are taken from each shoulder region, with the electrodes paired across the root of the arm, the ventricular deflections from the right side are, as a rule, very small, whereas those from the left are of much greater amplitude, with a few exceptions as noted in the text.

3. Ventricular complexes in leads taken on the left side of the body to the suprasternal notch from the arm and from the  $C_5$  position, and to the top of the shoulder from the axilla (across the root of the arm) show a remarkable correlation with each other, with Lead I, and with  $CR_5$ . Leads taken from comparable positions on the right side show no analogous correlations.

4. When the relative size of the auricular complexes from the two shoulder regions is compared with that of the ventricular complexes, a definite difference is noted. The auricular complexes, instead of being larger on the left, are, on the average, of approximately equal size.

5. The foregoing observations suggest that changes in potential in the region of the left arm exert a predominating influence in the formation of the ventricular complex of Lead I, and that these potential variations, in turn, are largely dominated by those arising from that portion of the ventricular muscle which governs the contour of the ventricular complex in the  $C_5$  position.

6. We are unable to account for our observations on the basis of the Einthoven equilateral triangle hypothesis. According to this concept, the extremities are far enough from the heart to permit it to function, in its relation to them, as an electrical point. This may be true of the right arm, for in the majority of cases there is little difference in the potential of adjacent areas in the vicinity of the right shoulder. However, the relatively large differences in the potential of adjacent areas in the vicinity of the left shoulder suggest that the left arm is too close to the heart, electrically, or at least to a portion of the left ventricle, to allow the heart to behave in relation to this extremity as Einthoven conceived that it would. Thus, the left arm must be regarded as a rather inferior chest lead position.

7. The fact that auricular deflections in right shoulder electrocardiograms are proportionately larger than ventricular deflections suggests

that, although the ventricles may be far enough from the right arm to function as an electrical point with regard to it, this is not necessarily true of the auricles.

8. Our observations do not in any way impair the usefulness of limb lead electrocardiography as an empirical procedure. However, it would seem advisable, at least for the present, to regard with a certain amount of skepticism the time-honored and elaborate, theoretical, electrocardiographic superstructure which has been erected upon Einthoven's assumptions, since there is now reason to doubt the complete validity of the two most important ones, namely, (1) that the body acts as a homogeneous fluid conductor, and (2) that the heart functions as an electrical point with regard to each of the three extremities.

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#### DISCUSSION

DR. LOUIS N. KATZ, Chicago.—Dr. Wolferth is to be congratulated for having joined those who are discarding the Einthoven triangle concept of vector analysis for general use and for having gone back to the older theory that Waller projected many years ago, when he recorded the human electrocardiogram for the first time.

A theory is valuable only insofar as it helps to advance knowledge. In the early days, the Einthoven triangle concept was useful. The facts that Dr. Wolferth presented show some of the fallacies of this concept; others we have pointed out in our work. The return to the old "field theory" offers many possibilities of obtaining new information without the handicap imposed by the theoretical, mathematical, and not too accurate concept of the equilateral triangle.

# THE USE OF THE CATHODE RAY FOR RECORDING HEART SOUNDS AND VIBRATIONS

## III. TOTAL CARDIAC VIBRATIONS IN ONE HUNDRED NORMAL SUBJECTS

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**I**N RECENT years phonocardiography has acquired a definite place in the diagnosis of heart disease. The registration of the heart sounds for clinical purposes was greatly facilitated by the introduction of electrical stethographs, whose convenience of use and superior accuracy in recording are signally superior to the older methods.<sup>1</sup> However, these stethographs have usually been constructed in such a way as to emphasize murmurs and other adventitious sounds. Such records may be of distinct value in studying certain adventitious sounds, especially as regards their relation to the cardiac cycle. Little, if any, attention has been paid to the general character of all of the vibrations produced by the heartbeat, the audible frequencies of which make up the heart sounds. As was pointed out in a previous communication,<sup>1</sup> certain fundamental changes in the heart tones may occur in various kinds and stages of heart disease; it would seem advantageous to record all of the vibrations set up by the heartbeat, both audible and inaudible, so that these fundamental changes, which may be obvious to the ear, can be recorded and studied.

The object of this communication is to present a composite study of tracings of total cardiac vibrations which were obtained from 100 normal young adults.

### PROCEDURE

The subjects were medical students and nurses, whose ages ranged from 20 to 35 years. All of them had previously had complete physical examinations, including roentgenograms of the chest, and were presumed to be in good health. The instrument used for recording the heart vibrations was the vibrocardiograph. A detailed description of the device has been presented.<sup>1</sup> In most cases the vibrocardiographic tracings were recorded simultaneously with Lead II of the electrocardiogram, and the records were synchronized by flashing lamps which played on the two records simultaneously.<sup>1</sup> During the procedure the subject lay supine for ten to fifteen minutes, until stability of the heart rate was assured. The blood pressure, which was recorded during the period of rest, was within normal range in each case. Tracings were obtained from the aortic, tricuspid, mitral, and pulmonie areas. In some cases the pickup unit was placed at other locations on the anterior chest wall, in an effort to discover whether there were variations in wave forms and intensities outside of the usual auscultation areas.

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## DESCRIPTION OF THE RECORDS

The dominant vibration groups in normal vibrocardiograms are those incident to the onset of systole (embodying the audible frequencies of the first heart sounds) and those incident to closure of the semilunar valves. In analyzing the first (systolic) vibration complex, a group of small preliminary waves (one to three in number) could usually be seen in records from all of the four auscultation areas. They were interposed between the P wave and the crest of the R wave, and immediately preceded the large principal vibrations of which the first sound is a part. The time of occurrence of the preliminary waves would seem to be just prior to the rise of intraventricular pressure at the onset of systole; they correspond in time to the "preliminary vibrations" noted by McKee.<sup>2</sup> It is possible that these ripples are caused by the forcible ejection of blood from the auricles into the ventricles during auricular systole. It is likewise possible that they may be induced by movements in the ventricular muscle when it is further distended by the force of auricular systole.

The main deflections follow the preliminary waves and consist of spikes of higher amplitude and frequency. These main deflections begin immediately after the peak of R and then taper into lower-frequency, lower-amplitude waves which finally disappear at, or just after, midsystole. Since the principal deflections include the audible components which comprise the first heart sound, the sound itself, therefore, falls on the descending limb of the R wave. The total duration of the first vibration complex, including the preliminary waves and the main deflections, with the audible frequencies, ranges from 0.19 to 0.29 second and averages 0.22 second when the heart rate ranges from 70 to 85 per minute. The duration of the main wave complex (i.e., deflections following the peak of R, including the audible portions) is from 0.08 to 0.19 second, and averages 0.11 second in the entire series of cases. The wide variation in the duration of the first vibration complex possibly depends on several factors, such as rapidity of rise of interventricular tension, thickness of the auriculoventricular valves, and the blood pressure level. It is interesting that, although subtle differences in the heart sounds may be detected in normal persons by auscultation, there may be striking variations in the shape of the waves of the first sound complexes among normal persons, as recorded by the cathode-ray oscillograph. Such changes appear to be caused by alterations in the lower-frequency components, without much visible modification in the sharp waves which produce the sound. It is likewise of interest that the shapes of successive waves from a given subject are remarkably constant, so long as the basal state remains undisturbed. The significance of the low-frequency components and other variations in the curves will be discussed later.

It is generally thought that the second heart sound is caused by the closure of the pulmonic and aortic valves. In the records obtained with the vibrocardiograph, or by ordinary phonocardiography, the second sound is sharper in profile and shorter in duration than the first sound complex. In this series, the second sound complex, both at the pulmonic and aortic areas, consisted of one to three sharp waves which ranged from 0.04 to 0.09 second in duration (averaging 0.06 sec.), with frequencies of approximately 80 to 90 d.v. per second. This is in agreement with the results obtained by most workers. The second sound complex falls on the descending limb of the T wave of the electrocardiogram. The amplitude of the deflections (sound intensity) is probably directly related to the level of the aortic and pulmonic pressure, as noted by Wiggers and Dean.<sup>3</sup>

General analysis of the duration of the vibrocardiographic curves with relation to the duration of systole, diastole, and the first and second sound complexes showed variable results. It is known that acceleration of the heart rate shortens diastole, and, occasionally, systole. A rise in blood pressure caused an increase in the duration of the first sound complex, apparently by prolonging that part which followed the peak of R. Age had some effect on the duration of the first sound. As a rule, the younger the subject, the shorter were the systolic vibration complexes, and, the older the subject, the longer were the systolic vibrations. The duration of the first vibration complex was generally shorter in female than in male subjects. The ratio of the duration of the first and second vibration complexes was roughly two to one, although, when the heart rate was fast, the two sounds frequently tended to be of the same duration. The point of contact also affected the ventricular complex; generally the vibrations at the aortic and tricuspid areas were more prolonged than at the pulmonic and mitral areas.

It is said that a third heart sound may occasionally be audible in early diastole, but none of our 100 subjects had a diastolic third heart sound. However, in 7 per cent of the tracings, there was, following the second sound complex, a large wave at the time when the third heart sound might be expected to occur (i.e., approximately 0.1 sec. after the second sound). The deflection was of too low a frequency to be heard. There is a general feeling that rapid ventricular filling in early diastole, producing sudden distension of the ventricular walls, creates vibrations which sometimes may be heard.<sup>4</sup> Hirsh and Gubner,<sup>5</sup> who studied cardiac movement by means of roentgenkymography, found that a sharp break occurs early in the diastolic wave from normal hearts. They interpreted this as representing sudden ventricular distension caused by rapid filling of the ventricular cavities. It would thus seem possible that sudden ventricular distension in early diastole

might produce a single movement which would register as a single, low-frequency wave.

Another group of subjects (5 per cent of the series) showed low-frequency, low-amplitude waves (below acoustic level) in diastole. There were usually three waves, although occasionally only two were evident. The phenomenon occurred principally in persons who had been athletes. It is curious that the diastolic waves were usually most marked in tracings made from the tricuspid or aortic areas. Occasionally they were more conspicuous when the receiver was placed at some point along the right sternal border. They appear to be the result of myocardial motion, as will be discussed later.

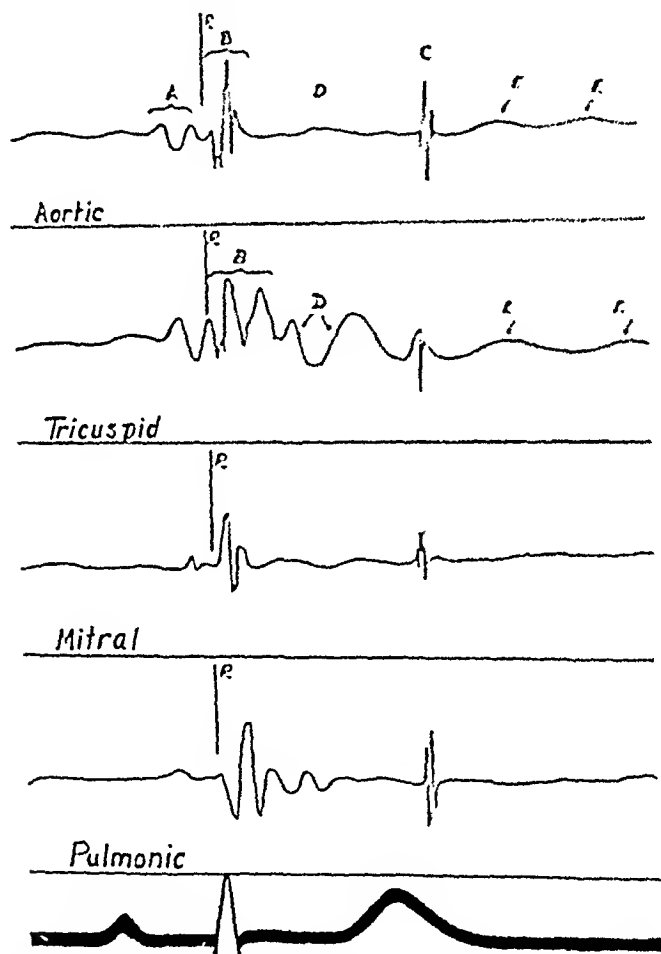


Fig. 1.—Diagrammatic sketch of typical vibrocardiographic curves in relation to Lead II of the electrocardiogram. The vertical line (E) represents the time of occurrence of the R wave. The preliminary waves (A) occur between P and R of the electrocardiogram. B indicates the "main deflections" at the onset of systole which embody the audible frequencies of the first heart sound. The peaked deflections (C) comprise the second heart sound. D and E are the low-frequency, inaudible waves which occur in systole and diastole.

In ordinary phonocardiography, murmurs and other adventitious sounds may appear particularly clear because of damping out of lower vibration frequencies and amplification of the higher; therefore,



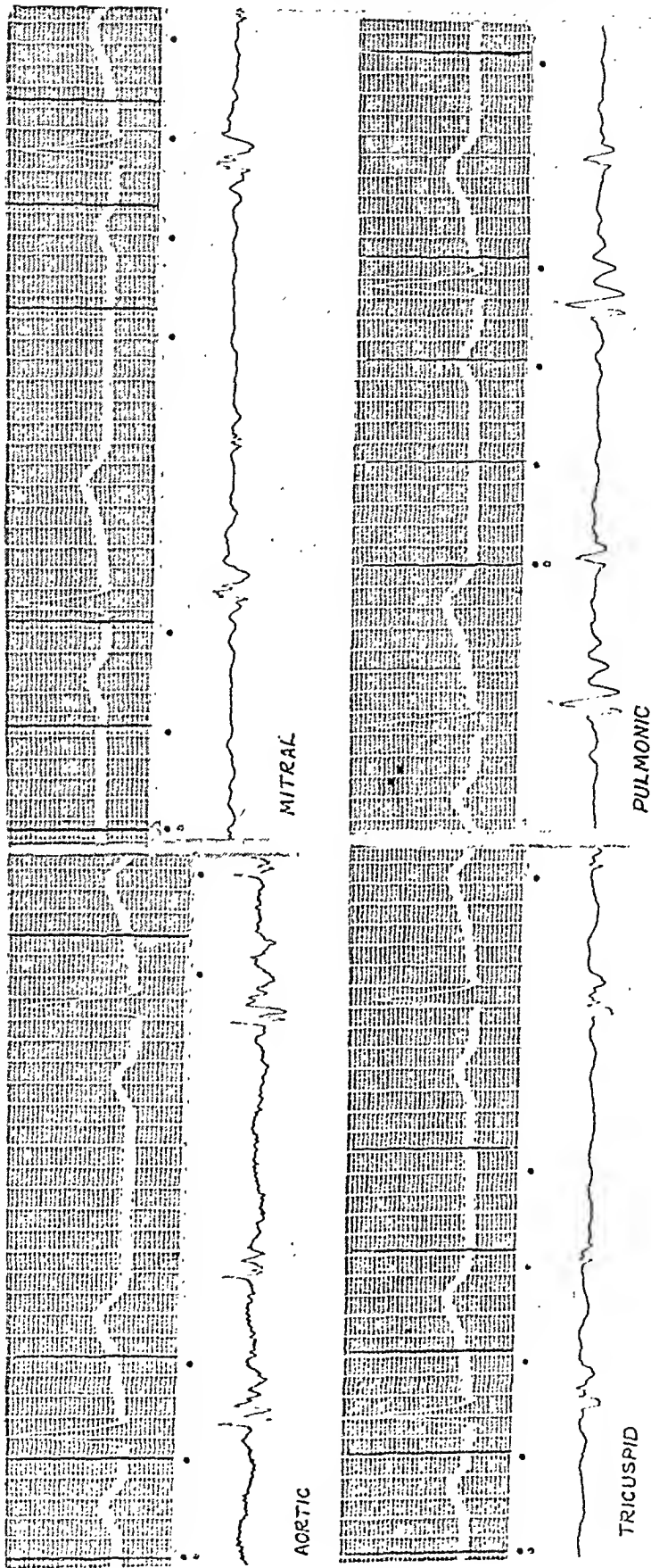


Fig. 2.—Vibrocardiogram of normal subject, synchronized with electrocardiogram (at approximately twice normal speed). The first and second sound vibration groups may be readily recognized. In each curve, low-frequency systolic undulations are seen, especially at the pulmonic area. The black dots on the vibrocardiogram and the black lines on the electrocardiogram represent intervals of 0.2 second; occasional interruptions in the lights indicate corresponding points on the records.

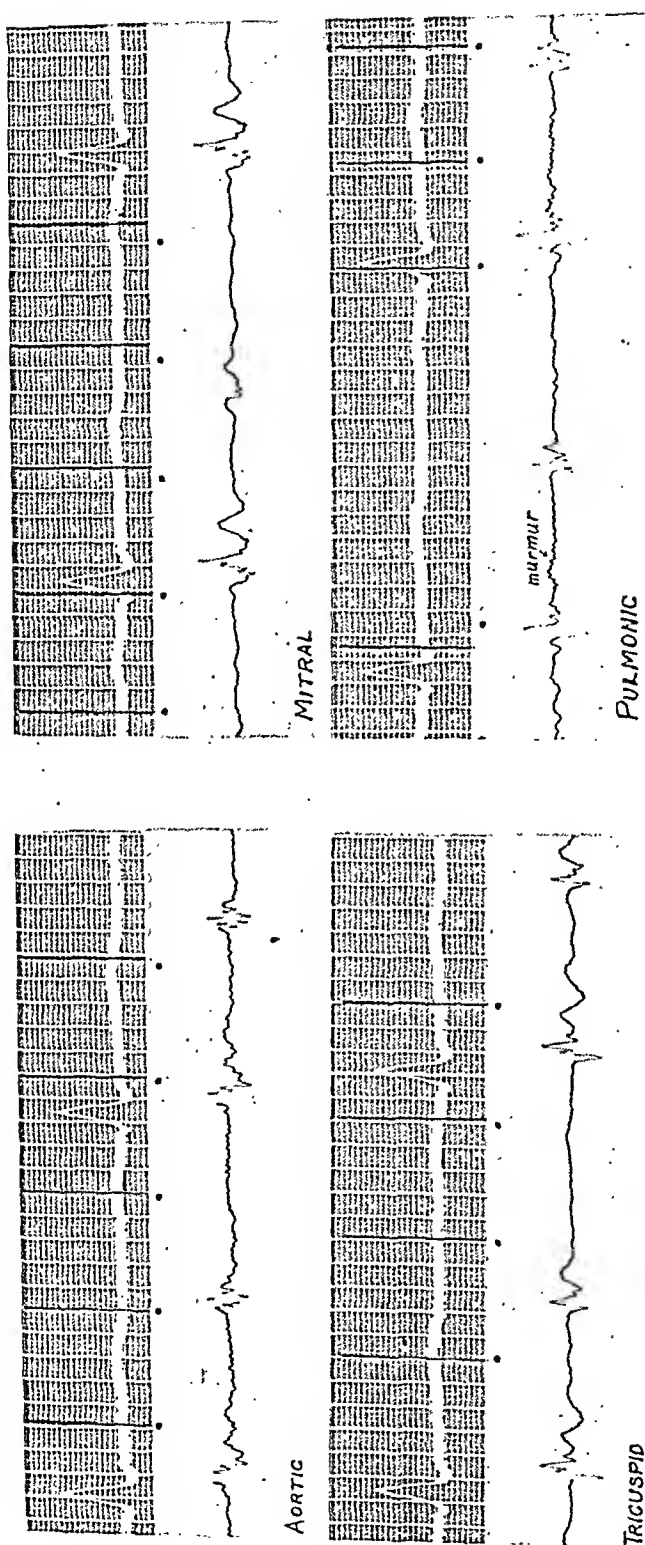


Fig. 3.—Synchronized vibrocardiogram and electrocardiogram of a normal subject. A faint, blowing, pulmonic systolic murmur was detected with the subject lying supine. Low-amplitude, high-frequency waves may be seen in the systolic interval of the record taken from the pulmonic area. As the murmur was of low intensity in comparison with the other heart sounds, it appears as diminutive waves in the tracing.

the deflections representing a murmur may be out of all proportion to the intensity at which they actually occur, as compared with the intensity of the heart sounds. Tracings obtained by this method will show that the vibrations incident to the murmur are of low amplitude if the intensity of the murmur is small in comparison with other sounds produced by the heartbeat. If, however, a murmur is loud, as in well-marked aortic stenosis, the sound may be registered as a series of tall, high-frequency, systolic waves. One frequently encounters pulmonic systolic murmurs in normal persons, especially when the subject is

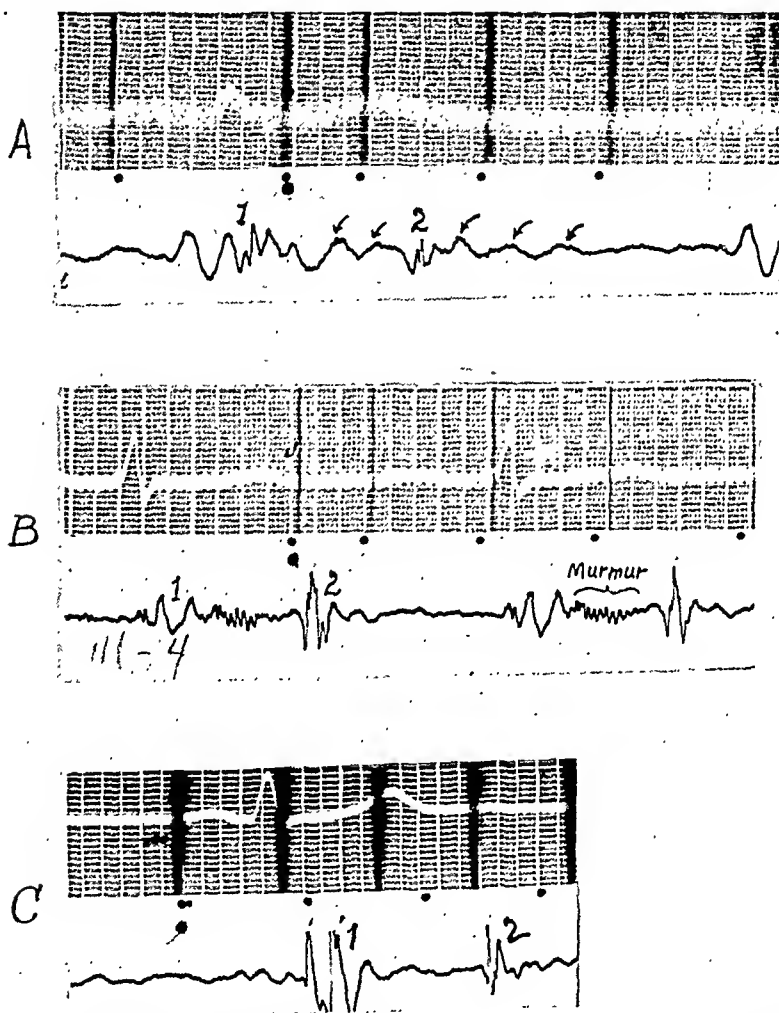


Fig. 4.—Vibrocardiographic curves, synchronized with Lead II of the electrocardiogram, picked at random from the series of cases. A, Curve obtained from the tricuspid area of a subject who showed low-frequency systolic and diastolic waves (marked by curved arrows). B, Curve obtained from the mitral area of a subject with a functional mitral systolic murmur. Note the high frequency systolic waves which represent the murmur. The intensity of the murmur is proportionate to that of the first and second sounds. C, Vibrocardiogram taken from the tricuspid area of a subject who had "splitting" or reduplication of the first heart sound. Note the two, tall, peaked waves, separated by a short segment; each wave has steep, audible slopes.

in the reclining position. This is best shown in Fig. 3; small, high-frequency waves are noted in the systolic intervals of the tracings obtained at the base of the heart. In this instance the murmur was faint; consequently, in the curve it is diminutive in comparison with the other waves.

An interesting occurrence in some normal hearts is splitting of the first or second sounds. In tracings recording total heart vibrations, this appears as a reduplicated or doubled series of tall deflections, with steep slopes as the audible portions (Fig. 4).

#### COMMENT

Curves were obtained from 100 normal subjects under as nearly uniform conditions as possible, and the tracings were generally similar. As noted before, the wave shapes may vary widely, although, to auscultation, the heart sounds may seem to differ but little. These variations in contour appear to be dependent largely on modification of the lower-frequency vibrations incident to ventricular systole. A survey of the material shows that the sharpness of the first vibration complex is not related to the duration of systole or diastole, for there may be shortened first sound vibration complexes when either systole or diastole is prolonged or shortened. However, it is recognized that the quality and intensity of the sounds may change in normal subjects, depending on the conditions under which the heart must work. Wiggers<sup>6</sup> found that, within certain limits, a change in the vibrations produced by the beating heart was an indication of a change in the rate of rise of intraventricular tension during the isometric phase of contraction. Thus, the speed and force with which the ventricle contracts, whether the subject is at rest or active, may determine the sharpness and intensity of the heart sounds. The heart tones may likewise be influenced by the size of the chest and the thickness of the chest wall. Obesity or a well-developed thoracic musculature may diminish the intensity of the vibrations, whereas in slender subjects the vibrations may seem particularly clear.

Of greater interest, we believe, than the recording of sound intensities and murmurs, are the low-frequency, inaudible deflections incident to the systolic and diastolic phases of ventricular contraction. The main vibrations of the first heart sound, or the tapering vibrations themselves, often embody such low-frequency waves. The cause of these systolic waves is not yet clear. Smith, Kountz, and Gilson,<sup>7</sup> working with hearts of dogs, noted that, when the auriculoventricular valves were immobilized, the vibrations produced by contraction of the myocardium alone were large and of low frequency, with slopes as steep as those of the audible vibrations. Such waves, as recorded from the beating dog heart, often bear a striking similarity to the low-frequency waves which are part of the first vibration complex in tracings from normal subjects. It is possible that these low-frequency waves indicate myocardial motion per se, and that they may result from additional contractile motions of the heart during systole.

Of equal interest are the low-frequency, low-amplitude diastolic waves which occur in some normal subjects, particularly in athletes,

As noted before, they are usually maximum at the aortic or tricuspid areas. In casting about for an explanation of this phenomenon, it first seemed likely that they might result from gross, pendulous motions of the heart, made possible by the mobility of the mediastinum and the resilience of the lungs. However, altering the position of the subject neither abolished nor accentuated the waves, although one might have expected a modification of the waves if a pendulous, swaying movement of the heart were a factor. It was also necessary to consider the possibility that the resonating properties of the chest might produce low-frequency waves incident to the heartbeat, but the deflections in question were found not to vary with respiration, nor to be influenced by tight strapping of the chest, which increased the resonating properties of the chest. It seems most likely, therefore, that the diastolic waves arise from motions of the myocardium itself. How such motion is produced, or why it occurs, is still a moot point. Recent work<sup>8-10</sup> suggests that diastolic waves may be caused by the passage of recoiling movements over the ventricular muscle, giving the appearance of a "notch-like" dilatation, rather than a smooth dilatation. If this were the case, one would expect such a phenomenon to occur universally. It is possible, however, that under some conditions they may be damped out.

#### SUMMARY

The usual study of heart sounds is limited to the recording of the sound vibrations only, with little attention to other vibrations produced by the beating heart. In this investigation, all of the cardiac vibrations at the usual auscultation areas in 100 normal young adults were recorded by means of a cathode-ray vibrocardiograph. The intensity and duration of the first and second sound vibration groups were studied in relation to the length of the systolic and diastolic phases of the cardiac cycle. With this method, murmurs are reproduced at the intensity with which they occur, and, if faint, may appear diminutive in comparison with the deflections which represent the heart sounds. Most interesting are the low-frequency vibrations, below the auditory level, which occur in systole and diastole and possibly indicate myocardial motion alone.

The authors wish to express their appreciation to the Burdick Corporation, whose cooperation made this work possible.

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## Department of Clinical Reports

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### ANTE-MORTEM DIAGNOSIS OF RUPTURE OF THE INTERVENTRICULAR SEPTUM AS A RESULT OF MYOCARDIAL INFARCTION

#### REPORT OF A CASE

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SAGER,<sup>1</sup> in 1934, collected from the literature seventeen cases of rupture of the interventricular septum as a result of myocardial infarction and added one of his own. Additional cases have since been reported by Gross and Schwartz,<sup>2</sup> Stern,<sup>3</sup> Stanley,<sup>4</sup> and Scott and Garvin.<sup>5</sup> In only three cases (Sager,<sup>1</sup> Stanley,<sup>4</sup> and Brunn<sup>6</sup>) was the diagnosis of rupture of the septum made before death. The case herewith reported brings the number of cases on record to twenty-three, and the number of correct ante-mortem diagnoses to four.

#### CASE REPORT

J. N. D., a white man, 47 years of age, was admitted to the medical service of the Charity Hospital of Louisiana on Nov. 20, 1939. Three weeks before, about thirty minutes after the noon meal, he had experienced a sudden, moderately severe, burning pain behind the upper part of the sternum. It radiated to the left shoulder and down the left arm and was accompanied by weakness and nausea. A physician who examined the patient shortly after the onset found nothing wrong with his heart, but told him that his blood pressure was high ("180 systolic"). The pain, which was attributed to indigestion, subsided completely within two hours, and after three days the patient was well enough to return to work. A few days later his physician again examined his heart and assured him that there was nothing wrong with it. His blood pressure at that time was 160/120.

A second attack occurred one week later, as the patient was on his way home from work. The pain at this time was confined to the left hypochondriac and epigastric regions and was of a moderately severe, burning character. It was accompanied by nausea, vomiting, weakness, and shortness of breath. Several hours after the onset the patient began to cough and to expectorate bloodstreaked sputum. An hour later his physician listened to his heart and told him that he had "heart trouble." A consultant who saw him at this time said that he had "a leak in his heart." He was advised to enter the hospital at once, but did not accept the advice until two weeks later. In the interim he remained in bed at home.

The patient had had semiannual physical examinations throughout the preceding five years and had felt entirely well until the onset of the present illness. During this period his systolic blood pressure had supposedly ranged between 160 and 180. No family history of heart disease could be obtained. He had had a penile lesion at the age of 27 years, for which he had been treated with injec-

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tions in the arm. On several occasions afterward he had been told that his blood Wassermann reaction was negative.

He was a rather poorly nourished patient, of asthenic habitus, who was supported by a back rest in the semirecumbent position. He was moderately dyspneic and seemed seriously ill. His temperature was 98.2° F.; his pulse rate, 82; his respiratory rate, 20 per minute; and his blood pressure, 120/100.

The pupils were circular, equal, and reacted promptly to light and in accommodation. The external jugular veins were moderately distended. There was slight dullness in the left subscapular region, and fine, moist râles were heard at the bases of both lungs posteriorly.

The cardiac apex impulse was in the sixth left intercostal space, about 9 cm. from the midsternal line. The pulsation was well localized and moderately forceful. A pronounced thrill was felt over the lower precordium, just to the left of the sternum. The first heart sound was not audible. The second sound was quite loud at the pulmonic area. A loud, rough murmur of medium pitch, which lasted throughout systole, was heard best 3 cm. to the left of the sternum in the fourth and fifth intercostal spaces and was transmitted over the entire precordium. The rhythm was normal.



Fig. 1.—Roentgenogram of chest, showing moderate cardiac enlargement and pulmonary edema.

The edge of the liver was 4 cm. below the right costal margin and was slightly tender. There was no edema over the sacrum or of the extremities.

Urinalysis showed a trace of albumin and a few erythrocytes. The erythrocyte count was 3,500,000; the leucocyte count, 8,050. The hemoglobin was 80 per cent (Sahli). The neutrophils numbered 66; the lymphocytes, 23; and the monocytes, 11 per cent. The blood Kline and Kolmer reactions for syphilis were negative.

A roentgenogram of the chest (Fig. 1), taken just after the patient was admitted to the hospital, showed a moderate, general enlargement of the cardiac



silhouette. The aortic knob was prominent, and there was calcification of the aorta. Dense mottling was seen throughout both bases and in the region of the hila of the lungs; this was interpreted as evidence of pulmonary edema. The left costophrenic angle was obliterated, probably by a small quantity of fluid. The first and last of several electrocardiograms which were taken during the period of hospitalization are presented in Fig. 2.

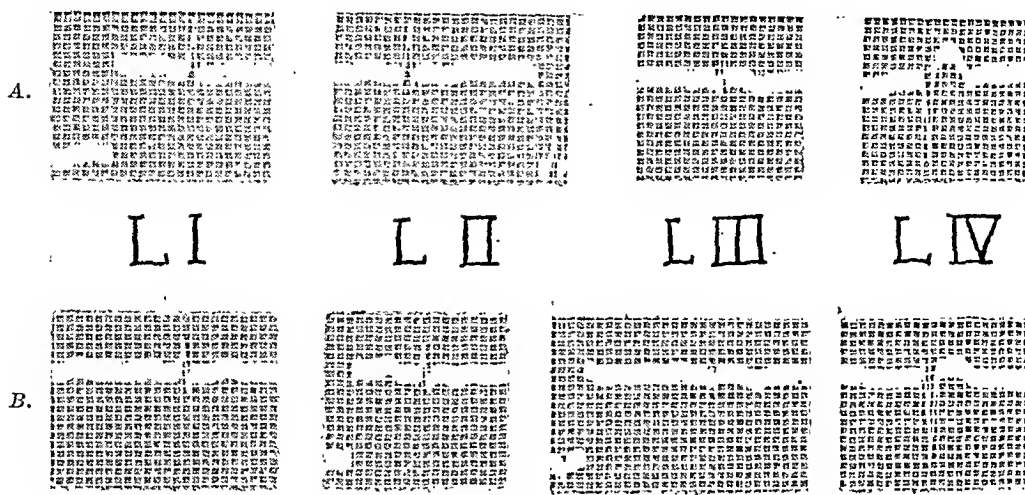


Fig. 2.—Initial and final electrocardiograms. A, Nov. 21, 1939. B, Jan. 2, 1940. Leads I, II, and III show  $Q_3$  and broad  $Q_3$ . Slight deviation to the right of the mean electrical axis of QRS has developed in the lower curve. Lead IV F shows absence of R (upper curve) and elevation of the RS-T junction.

Two weeks after the patient was admitted to the hospital edema appeared in the lower extremities. The administration of digitalis, which had been given continuously, was discontinued at this time because of nausea and vomiting. With the appearance of the edema, the distention in the neck veins increased, the apex impulse became diffuse, and the left border of cardiac dullness extended to the left anterior axillary line. The blood pressure was 120/86. During inspiration, the border of the liver descended 8 cm. below the right costal margin.

There was a transient response to treatment with a neutral-ash, salt-poor diet, ammonium chloride, salyrgan, and restricted doses of digitalis, but congestive heart failure soon became marked. Ascites developed; edema of the chest and abdominal wall appeared; the sclerae and the skin of the head and neck became icteric (index 18); and the dullness and râles at the bases of both lungs became more marked. The precordial thrill and murmur remained unchanged throughout the illness. Death occurred eight weeks after admission to the hospital.

*Ante-Mortem Diagnosis.*—A diagnosis of rupture of the interventricular septum as a result of myocardial infarction was made shortly after the patient was admitted to the hospital, for the following reasons: The history and electrocardiographic changes were thought to be sufficient to establish the diagnosis of hypertensive and arteriosclerotic heart disease, with cardiac infarction. Inasmuch as left axis deviation might be expected in a case of hypertension which had lasted five years or more, the form of the patient's electrocardiogram was considered indicative of some further abnormality. The changes in Leads I, II, and III indicated injury to the diaphragmatic wall of the left ventricle and neighboring portion of the interventricular septum.<sup>7</sup> On the other hand, the QRS complex of Lead IV F was considered diagnostic of infarction of the anterior wall of the left ventricle near or at its apex. The upward displacement of the

RS-T junction and segment in this lead was regarded as indicative of recent injury in the anterolateral wall of the left ventricle.



Fig. 3.—Anterior view of the heart, showing aneurysmal dilatation of the ventricular apex. The descending branch of the left coronary artery has been opened.



Fig. 4.—View of the heart looking into the left ventricle toward the interventricular septum, which appears white and fibrotic throughout its lower third. Three septal perforations are seen just above the lower glass rod.

A thrill and a loud systolic murmur over the center of the precordial region are characteristic signs of a defect in the interventricular septum. The fact that these signs, according to the patient's history, had only recently appeared, to-

gether with the whole clinical picture and the electrocardiographic evidence, made it appear almost certain that rupture of the septum, near the apex, had occurred. The development of high-grade, right-sided heart failure after the patient entered the hospital, and the small but definite  $S_1$ , lent still further support to the diagnosis of rupture of the interventricular septum.

*Autopsy.*—Post-mortem examination revealed a moderately enlarged heart and an aneurysmal dilatation of the apex of the left ventricle (Fig. 3). The heart weighed 485 Gm. The wall of the basal region of the left ventricle measured 14 mm. in thickness, but the wall of the aneurysmal sac at the apical region measured only 2 mm. The right ventricular wall was 10 mm. in thickness in the basal region, and 7 mm. in the apical region. The mitral valve admitted two fingers with ease; and the tricuspid valve, the tips of four fingers. The pulmonary conus was slightly dilated. The first portion of the aorta was of normal size; it exhibited moderately severe atherosclerosis. The basal region of the interventricular septum bulged moderately into the chamber of the left ventricle and thus formed part of the dilated infundibulum of the right ventricle. The apical third of the interventricular septum formed the right lateral wall of the aneurysmal sac at the apex of the left ventricle and protruded into the apical region of the right chamber for a distance of 2.75 cm. At the apex of this protrusion there were three irregular openings (Fig. 4) which connected the two chambers. The total area of the openings was approximately 2.5 sq. cm.

The entire inner surface of the aneurysmal sac was white and densely fibrotic, as might be expected ten to eleven weeks after infarction. The aneurysm, in addition to involving the apical third of the interventricular septum, extended upward from the apex on the anterior left ventricular wall for a distance of 4.5 cm. and upward from the apex on the posterior left ventricular wall for a distance of 1.5 cm.

Arteriosclerosis had caused marked narrowing of the first part of the right coronary artery and moderate narrowing of the left coronary artery. No area of total occlusion was found.

#### COMMENT

The diagnosis of rupture of the interventricular septum as a result of cardiac infarction, although it has been made in only four of the twenty-three reported cases, including the case herewith reported, should in most instances be quite simple. It depends chiefly upon keeping in mind the possibility of rupture when a patient presents the clinical manifestations of cardiac infarction and the precordial signs of a septal defect. If it can be established by the history or by observation that the latter appeared after the onset of the infarction, the diagnosis is almost certain. If the patient survives the acute stage, the appearance of high-grade, right-sided congestive heart failure supports the diagnosis of septal rupture and helps to exclude the possibility of a torn papillary muscle. The development, after the acute stage, of deviation to the right of the mean electrical axis of QRS offers a measure of confirmation to the diagnosis of septal rupture.

#### SUMMARY

1. A case of rupture of the interventricular septum as a result of cardiac infarction is added to the twenty-two others already on record in the literature.

2. A correct ante-mortem diagnosis was made in this case, bringing to four the number of cases in which the condition was recognized before death.

3. The considerations which led to the ante-mortem diagnosis are outlined, and it is pointed out that, although the condition is rare, it should be diagnosed if the physician bears the possibility in mind when he is confronted with a patient who presents the clinical manifestations of cardiac infarction and the precordial signs of a septal defect.

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# ACUTE RHEUMATIC HEART DISEASE IN THE AGED

## REPORT OF A CASE WITH UNUSUAL CLINICAL MANIFESTATIONS

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### INTRODUCTION

THE acute rheumatic state is generally regarded as a childhood disease, usually associated with cardiac involvement. Leonard,<sup>1</sup> who studied a large series of cases (500), reported that the highest incidence of initial attacks occurred between the ages of 5 and 11 years, and that 71 per cent of the patients developed rheumatic heart disease and suffered most of their recurrences before puberty. Juster,<sup>2</sup> in an exhaustive study of fifty-nine patients with chronic rheumatic heart disease between the ages of 15 and 44 years, demonstrated that reactivation of the rheumatic carditis was a usual and common occurrence, but Rothschild<sup>3</sup> and his collaborators, in a series of 161 cases of chronic rheumatic heart disease, noted activity only twice in the sixth decade and but once in the seventh decade. In this latter case, that of a woman of 62 years, there was evidence of old coronary occlusion and recent bronchopneumonia. Thus, active rheumatic carditis is rare in the later decades of life, yet in the following case there was a widespread, uncomplicated, active, rheumatic myocardial inflammatory process in a woman of 61 years which caused her death after extraordinarily confusing clinical manifestations.

### CASE REPORT

M. L., a white widow, 61 years old, had been in excellent health as long as she could remember. She was 5 feet 5 inches in height and weighed 150 pounds. At no time did she recall having any symptoms of the rheumatic state, nor had any cardiac lesion ever been discovered. Only once did she require medical service, and this was during her only pregnancy (which was normal), when she was 20 years old. The child had the usual diseases of childhood, but nothing indicative of rheumatism, and is now a healthy, 40-year-old man. The patient worked in a shirt factory for many years until Feb. 13, 1939, when she developed an attack of tonsillitis, associated with high fever, a feeling of exhaustion, and severe bodily aches. The following morning a severe earache began, and, within twelve hours, there was a discharge from the left ear, but the pain persisted. An otolaryngologist discovered rupture of the ear drum and advised irrigations of the external auditory canal. Two days after the onset her temperature had returned to normal and her condition was greatly improved. The discharge from the ear gradually subsided, and ended on the tenth day, when the patient returned to work, apparently well.

One week later, vague pains in the wrists were experienced for the first time; these lasted for a few days. There was no swelling of these or any other joints. On March 16 slight dyspnea on exertion developed, but grew no worse until 4 A.M., March 19, when she was awakened by a severe attack of dyspnea, accompanied by

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cyanosis and pulmonary edema. Relief immediately followed the administration of 10 c.c. of aminophyllin intravenously, together with a hypodermic of  $\frac{1}{4}$  grain of morphine sulfate. Thirty-six hours after this attack of nocturnal dyspnea there were a fever of  $103^{\circ}$  F. and a very painful polyarthrititis, involving chiefly the wrists and shoulder joints.

Upon admission to the City of Kingston Hospital on March 20, 1939, the temperature was  $103.4^{\circ}$  F., the pulse rate was 110, with numerous premature systoles, and the blood pressure was 138/80 mm. Hg. Both wrists were swollen, red, and painful, and there were pain and limitation of motion of the shoulder joints. A few scattered petechiae were present in the skin over the abdomen and left forearm. The heart was not enlarged to percussion, but there was a soft, apical, systolic murmur of moderate intensity which was not transmitted, and the pulmonic second sound was accentuated. The liver extended 3 cm. below the right costal margin and was slightly tender, but no pulsation could be felt. Râles were heard at the bases of the lungs, and there was moderate edema of the lower extremities. Dyspnea and orthopnea were marked, but the cyanosis had disappeared. There were no other significant physical signs. The tonsils were small and not inflamed, and the eye grounds were not remarkable. The erythrocytes numbered 3,300,000 per cu. mm., and the hemoglobin was estimated as 10 Gm. per 100 c.c. A rather marked leucocytosis was present (23,650, 88.5 per cent of which were polymorphonuclears). There was a pronounced albuminuria, and the urinary sediment contained a few erythrocytes, some granular and hyaline casts, and large numbers of leucocytes. There was no nitrogen retention in the blood except for a uric acid value of 5.0 mm. per cent. The blood chloride and cholesterol content was within normal limits, and a blood culture yielded no growth after two days' incubation. Roentgenologic studies of the paranasal sinuses, mastoids, and lungs showed nothing abnormal. The cardiac shadow was not enlarged, nor was there any accentuation of the pulmonary conus. Electrocardiograms confirmed the clinical impression that there were many premature ventricular systoles, but otherwise showed nothing of importance. There was no axis deviation, and the P-R interval was not prolonged. At this time a tentative diagnosis of subacute bacterial endocarditis was made, in spite of the fact that organisms had not been isolated from the blood and no history or physical evidence of previous cardiac disease could be obtained.

The course of the disease, which extended over a period of seven weeks, was not characteristic of subacute bacterial endocarditis, but no other plausible explanation for the clinical manifestations in a patient 61 years of age came to mind. The possibility of generalized lupus erythematosus was considered, but because of the continued absence of any skin manifestations and the wide dissimilarity between the clinical signs and those of the Libman-Sacks syndrome, it was felt that this could be ruled out.

The temperature was of the undulating type; it rose at two-week intervals to  $103^{\circ}$  F. and then gradually fell to slightly above the normal level, but at no time returned to normal. Large doses of neoprontosil had no effect on the hyperpyrexia. The leucocyte count ranged from 14,500 to 23,000 per cu. mm. Albumin, moderate numbers of erythrocytes, and leucocytes persisted in the urine. Four blood cultures, taken at regular intervals, remained sterile after nine days' incubation. The anemia did not progress.

No increase in the size of the heart was ever detected; the systolic murmur was inconstant, but never increased in intensity or changed in quality. The pulmonic second sound became somewhat louder, and there were long intervals when no extrasystoles could be detected. Several subsequent electrocardiograms were the same as that taken upon admission; at no time did they reveal evidence of myocardial disease. The peripheral edema and the dyspnea responded slightly, if at all, to adequate

digitalization, but great improvement followed the administration of aminophyllin parenterally.

After two weeks' rest in the hospital the arthritic manifestations had practically subsided, and then there was a rather sudden exacerbation of the symptoms, involving the same joints.

The most striking feature of her illness was the seven attacks, all of which were essentially the same, of sudden dyspnea, followed rapidly by cyanosis and signs of pulmonary edema. The first six of these attacks responded very well to aminophyllin, given intravenously, and morphine, given subcutaneously, but the seventh was fatal.

#### POST-MORTEM EXAMINATION

The body was fairly well nourished. There was no edema. Faded petechiae were seen on the chest and arms, but not more than six or eight, in all, could be recognized. The liver was moderately enlarged and markedly congested, and, upon section, showed very prominent lobulations like those found in chronic passive congestion. The spleen was not remarkable; its pulp was firm and brownish red, in no way resembling chronic splenic tumor. No petechiae were found in the kidneys, intestines, or other abdominal viscera. The heart was slightly enlarged; it weighed 350 Gm. and was bathed by an increased quantity of clear, straw-colored fluid. There was no exudate on the epicardium, but it presented a dull, grayish appearance which, upon close inspection, was found to be caused by minute, discrete, grayish areas under the serosal surface. The cardiac hypertrophy was limited entirely to the slightly dilated left ventricle. The mitral valve was moderately thickened, and its chordae tendineae were somewhat enlarged and shortened. Along the line of closure many minute, almost transparent vegetations appeared. These vegetations were precisely like those which occur in acute rheumatic heart disease. It was very striking how the small blood vessels in the myocardium stood out as whitish lines. When these were cut across, they appeared as whitish oval and circular nodules. The aortic cusps were slightly stiffened, and, along the line of closure, there were the same minute, translucent vegetations. The tricuspid valve, except for slight thickening, showed no significant alteration. The coronary vessels were patent down to the smallest visible division, but, in places, the wall was concentrically thickened at the expense of the lumen, and much of this thickening was intimal. There were no scars in the myocardium which in any way suggested that vascular occlusion had occurred. The aorta was altered by thick intimal patches around the orifices of the coronary arteries, but otherwise showed nothing. Each pleural sac contained approximately 500 c.c. of clear fluid, and the lungs were the seat of rather marked edema. They were pale in color and showed no evidence of long standing passive congestion; there was no gross evidence of consolidation.

Histologic studies revealed the largest and greatest number of Aschoff bodies in the myocardium that we have ever seen. The inflammatory process had actually destroyed large areas of muscle fibers and extended to the endocardium and epicardium. All of the muscle fibers were swollen and stained poorly, and many were fragmented. Their nuclei were large and vesicular. MacCallum's patch on the wall of the auricle was large, but not very conspicuous grossly; yet the sections revealed large numbers of Aschoff cells spreading apart the fibromuscular bundles in this area. The acute rheumatic vegetations on the mitral and aortic valve leaflets were typical. There was evidence of at least one previous attack of rheumatism in the form of old scarring and vascularization of the mitral valve. It was only after some search that perivascular scars, thought to be old, healed Aschoff bodies, could be found in the myocardium. Changes in the coronary vessels were quite evident. Large numbers, but not all, of the vessels about the size of the Thebesian vessels had swollen endothelial cells and edematous walls. Vessels of the magnitude of arterioles showed many areas of intimal thickening, edema, and cellular infiltration

of the adventitia. Rarely, the lumen was completely occluded. Alterations in the larger coronaries were essentially those of arteriosclerosis, with marked intimal thickening by old fibrous tissue, in which fat-laden cells were imbedded. Aschoff bodies were found in the fat surrounding the larger coronaries, but only mononuclear cells infiltrated the adventitia. Merely by chance, slides were prepared from the aorta; they showed two distinct acute rheumatic nodules in the adventitia. The sinusoids of the liver were widened, without perivascular scarring, and there was edema of the lungs.

#### COMMENT

During the initial rheumatic infection, which doubtless occurred in childhood, the illness probably was minimal, and the injury to the myocardium and valvular endocardium so slight that it was never recognized. Not until the patient developed acute congestive heart failure, at the age of 61 years, did she ever present any obvious symptoms or signs of cardiac disease. Although heart failure as the result of active carditis in cases of chronic rheumatic heart disease is common in the earlier decades of life, it is indeed rare in the later decades, in which heart failure is caused by some added factor, such as hypertension or coronary thrombosis. The absence of marked cardiac hypertrophy, significant valvular inadequacy, hypertension, and coronary artery sclerosis leads us to believe that this patient's congestive heart failure was caused solely by the active myocardial inflammation, evidenced by great numbers of huge Aschoff bodies which had destroyed large areas of muscle, swelling of the intact muscle fibers, and acute rheumatic lesions in the small coronary blood vessels.

Cardiac hypertrophy is a usual sequel of chronic congestive heart failure. Stretching of the fibers is the stimulus to hypertrophy. Hypertrophy is said to result regardless of whether the congestive failure is caused by a mechanical factor (hypertension, valvular distortion) or infectious myocarditis. This case, with its evidence of a severe, acute myocardial inflammation, leads us to doubt whether acute myocarditis, per se, can cause cardiac hypertrophy. The slight hypertrophy which was found might well be ascribed to mechanical strain produced by pre-existent distortion of the mitral valve.

#### CONCLUSION

A case of acute rheumatic fever in a woman 61 years of age, with extensive, acute, rheumatic myocarditis, is reported. Attacks of paroxysmal nocturnal dyspnea, associated with congestive heart failure, were the outstanding clinical features.

#### REFERENCES

1. Leonard, Marion: Puberty and Prognosis in Rheumatic Fever, *AM. HEART J.* 14: 192, 1937.
2. Juster, I. R.: The Significance of Rheumatic Activity in Chronic Rheumatic Heart Disease, *AM. HEART J.* 15: 1, 1938.
3. Rothschild, M. A., Kugel, M. A., and Gross, L.: Incidence and Significance of Active Infection in Cases of Rheumatic Cardiovalvular Disease During Various Age Periods, Clinical and Pathological Study, *AM. HEART J.* 9: 856, 1934.



# Department of Reviews and Abstracts

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## Selected Abstracts

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Harington, C. R., Pochin, E. E., and Squire, J. R.: A Simplification of the Evans Blue Method of Blood Volume Determination. Clin. Sc. 4: 311, 1940.

A method is described by which Evans blue can be extracted from plasma into butyl alcohol.

The dye can readily be estimated photoelectrically or colorimetrically in the final extract, which is free from plasma pigments and opacity.

The technique has been applied to the estimation of blood volume in fifteen normal individuals.

AUTHORS.

Wiggers, Carl J., and Wégria, René: Quantitative Measurement of the Fibrillations of the Mammalian Ventricles With Observations on the Effect of Procaine. Am. J. Physiol. 131: 296, 1940.

The methods used for determining variations in the sensitivity or resistance of the ventricles to fibrillating agents are briefly reviewed and reasons presented why they are inadequate.

A new quantitative measure for the "fibrillation threshold" of the ventricles is proposed and tested. We believe it takes into account the irritability of non-refractory myocardial fractions during the vulnerable phase of systole, and also any local state that may be necessary for the initiation of ventricular fibrillation. The procedure consists in measuring the current strength of brief D. C. shocks of constant duration (0.01 to 0.03 sec.) which are just able to induce fibrillation when applied during the vulnerable period of late systole to any fixed region of the ventricular surface.

The coefficients which modify the constancy of such thresholds were studied, and it was established that, despite repeated fibrillations and defibrillations, the threshold need not vary significantly and does not change abruptly over a period of four to five hours in untreated dogs. To obtain such relative constancy of fibrillation thresholds, the following conditions were observed: 1. Revival of the heart from fibrillation in less than thirty seconds. 2. Maintenance of the animal's blood temperature within 1 to 2° C. during the course of an experiment, which essentially determines surface temperature as well. 3. Stimulation at the same spot by D. C. shocks applied in alternate directions through nonpolarizable electrodes. 4. Allowance of an equilibration period of not less than fifteen minutes between one fibrillation and resumption of tests.

The applicability of the quantitative method was tested with reference to procaine which is reputed to increase the resistance of the ventricle to certain fibrillating agents. In six dogs, an increase in threshold, definitely beyond normal bounds was found; after treatment with procaine, a brief shock still fibrillates only when it is applied during the vulnerable period. We concluded that procaine raises the resistance of the ventricles to fibrillation but does not prevent its occurrence.

AUTHORS.

Wiggers, C. J., Wégria, R., and Piñera, B.: The Effects of Myocardial Ischemia on the Fibrillation Threshold—The Mechanism of Spontaneous Ventricular Fibrillation Following Coronary Occlusion. *Am. J. Physiol.* 131: 309, 1940.

Alternate determinations of the fibrillation threshold of ventricles with a normal blood supply and during brief coronary occlusion were repeatedly made on the same animal. Rectilinear shocks 0.01 to 0.02 second in duration were applied to an identical area of the left ventricle. The milliamperage value of a shock which, when applied during the vulnerable phase, induced fibrillation, served as the quantitative measure of the fibrillation threshold.

Significant reduction in the current strength required to fibrillate was noted during coronary occlusion, e.g., a decrease from 13.9 to 3 Ma. in one experiment. The vulnerable period of the ischemic region does not bear a normal relation to the ventricular pressure curve because the contraction of fibers in the ischemic area does not contribute to the pressure elevation and because the form and duration of the pressure curve are altered. Consequently, stimuli coinciding with the descending limb fibrillate, but those which fall on the horizontal portion of the pressure curve are ineffective in this respect.

The observations of Tennant and Wiggers that the ischemic area no longer shortens but stretches during systole cannot be interpreted as a complete failure of the effort contraction, but rather that the strength of effort is insufficient to overcome the stretching force of rising intraventricular pressure. When this force is removed during fibrillation, contractile waves are able to manifest themselves again.

Since ischemia reduces the fibrillation threshold to artificial stimuli and also causes formation of ectopic centers, the theory is put forward that such ectopic stimuli now become of threshold value for the hyperirritable myocardium and any one is capable of inducing fibrillation when it falls during either the vulnerable period of a normal beat or that of a premature beat excited from another ectopic center.

AUTHORS.

Goldberg, Harold, and Eyster, J. A. E.: The Relation of Contraction of Different Regions of the Ventricle of the Turtle to the Rise of Intraventricular Pressure. *Am. J. Physiol.* 131: 416, 1940.

The rise of pressure in the ventricle of the turtle during systole is characterized by an initial slow rise, amounting to a few millimeters of mercury and lasting about 0.12 second. This is followed by an abrupt increase of the pressure gradient. Local shortening of various regions on the anterior surface of the ventricle begins during the initial period of pressure rise or within an interval of several hundredths of a second after its termination. Shortening in all regions thus occurs before the pressure has risen sufficiently to force blood into the great vessels and reduce the volume of the ventricle. This shortening is made possible by change in shape of the ventricle early in its contraction to approximate that of a sphere. Myograms from the surface of the ventricle of the turtle hence afford an adequate criterion for the onset of the local shortening process and for a comparison of electrical and mechanical events.

AUTHORS.

Dow, Philip: The Development of the Anacrotic and Tardus Pulse of Aortic Stenosis. *Am. J. Physiol.* 131: 432, 1940.

The anacrotic halt and tardus characteristics of the radial pulse in cases of aortic stenosis are shown to be due to the following factors:

1. Stenosis so reduces the violence of the systolic discharge that standing waves are not set up and the peripheral pulse reproduces the central pulse form with almost complete faithfulness.

2. The stenosis offers so much resistance to flow during mid-systole that the central pulse itself assumes the anacrotic and tardus characteristics.

AUTHOR.

Hedley, O. F.: Rheumatic Heart Disease in Philadelphia Hospitals. Public Health Reports 55: 1707, 1940.

Of the 5,921 admissions involving rheumatic heart disease, rheumatic fever, Sydenham's chorea, and subacute bacterial endocarditis to Philadelphia hospitals from Jan. 1, 1930, to Dec. 31, 1934, 1,020 or 17.2 per cent, are known to have terminated fatally during the period under study or during an admission begun prior to Jan. 1, 1935. Excluding subacute bacterial endocarditis, apparently not superimposed on rheumatic heart disease, death occurred in 916, or 15.8 per cent of 5,801 admissions for rheumatic conditions. Of 4,653 cases, in contradistinction to admissions, of rheumatic conditions and subacute bacterial endocarditis, 1,020 or 21.9 per cent died. Excluding subacute bacterial endocarditis apparently not superimposed on rheumatic heart disease, 916 or 20.2 per cent of 4,538 cases resulted fatally.

Of the 916 fatal cases of rheumatic heart disease, 94.0 per cent were admitted primarily for rheumatic conditions or subacute bacterial endocarditis superimposed on rheumatic heart disease.

The cause of death of only 1.6 per cent of 916 fatal clinical cases of rheumatic heart disease appeared to be attributable directly to causes other than rheumatic heart disease or subacute bacterial endocarditis as a complication. Had this study been made on the basis of post-mortem examinations rather than clinical cases of rheumatic heart disease, this percentage in all likelihood would have been substantially increased.

With one possible exception the cause of 916 deaths involving rheumatic conditions, including subacute bacterial endocarditis as a complicating factor, was rheumatic heart disease. In no instance was death attributable to the arthritic manifestations of rheumatic fever or the cerebral manifestations of Sydenham's chorea.

Most deaths from rheumatic heart disease among patients who have been hospitalized occur in hospitals; almost three-fourths of the fatal cases are admitted only once.

The mean age at death from rheumatic heart disease, regardless of its association with subacute bacterial endocarditis, in both clinical and necropsy series is slightly less than 30 years. A slightly greater proportion of deaths is indicated among females than among males. Taking into consideration the less favorable economic circumstances of negroes, the proportion of deaths from rheumatic heart disease in hospitals among members of this race was not as great as might be expected. This is probably influenced by the age distribution of the negro population as a result of migration in recent years. The mean ages and age distributions do not suggest as great differences on the basis of race and sex as encountered in certain other types of heart disease.

Among 916 deaths from rheumatic heart disease, including subacute bacterial endocarditis as a complication, the greatest number occurred during the 20 to 29 year age period, with nearly as many in the 10 to 19 and 30 to 39 year age periods. Over 63 per cent occurred during these three age decades.

Over 50 per cent of deaths from rheumatic heart disease occurred among persons less than 30 years of age, while only 3 per cent occurred among persons over 60 years of age. Unlike many forms of heart disease, practically all deaths from rheumatic heart disease occur before the expiration of a normal span of life.

The age distribution of 732 deaths from rheumatic heart disease, exclusive of subacute bacterial endocarditis as a complication, manifested a double humped curve with peaks in the 10 to 19 and 30 to 39 year age decades.

Over 75 per cent of the deaths from rheumatic heart disease among persons under 30 years of age were apparently due to active rheumatic infection. Rheumatic infection is almost invariably the cause of death in children and young persons. With advancing age it becomes a less significant factor.

Peak of deaths from subacute bacterial endocarditis, regardless of its relationship to rheumatic heart disease, occurred during the 20 to 29 year age decade. The distribution by age decades and mean ages at death indicated death at ages younger by several years from subacute bacterial endocarditis superimposed on rheumatic heart disease than from other forms of subacute bacterial endocarditis.

These studies do not suggest that deaths from rheumatic heart disease in Philadelphia hospitals are more common among persons foreign born or of foreign extraction from among old-stock white Americans; if anything, the opposite obtains. This is probably influenced by the readiness with which various racial groups avail themselves of hospital facilities, their economic status, and the relative age of foreign groups, which is dependent in no small measure on the period of greatest immigration.

From the distribution of deaths by socioeconomic groups it is inferred that fatalities from rheumatic heart disease are disproportionately high among the laboring classes. Few deaths were indicated among professional men. In rheumatic heart disease choice of occupation is often limited because the disease develops during childhood; as a result persons with rheumatic heart disease are not as likely to engage in occupations requiring strenuous exertion as their social status would otherwise suggest.

Rheumatic heart disease results in approximately 200 deaths in Philadelphia hospitals annually; 165 are due primarily to rheumatic heart disease, while 35 are due to subacute bacterial endocarditis superimposed on rheumatic heart disease. In about 0.10 per cent of admissions from all causes, death is due to rheumatic heart disease.

Definite histories of rheumatic fever, Sydenham's chorea, or both of these conditions were obtained in 66.2 per cent of fatal cases. In nearly 80 per cent of instances in which the age at onset was given, the primary rheumatic manifestation developed prior to age 20 years; in less than 3 per cent was onset indicated among persons past 40 years of age.

The mean age at onset was 14.7 years, the mode, 9.3 years. The mean interval between the primary rheumatic manifestation and death was 12.4 years. Among 542 fatal cases in which the duration was ascertained, death resulted in less than one year in 13.5 per cent, in less than five years in nearly 32 per cent, and in less than ten years from the onset of the primary rheumatic manifestation in over 48 per cent.

At least 3.5 to 4.5 per cent of first attacks of rheumatic fever terminated fatally. If deaths from fulminating rheumatic carditis without arthritic manifestations of rheumatic fever are included, the percentage of initial case fatalities becomes even higher.

Despite the pre-eminence of Philadelphia as a medical center, mortality from rheumatic heart disease among hospital patients constitutes a distinctly local problem; at least 87.2 per cent of fatal cases were residents.

Nearly 8 per cent of deaths from rheumatic heart disease required investigation by the coroner's office because of their suddenness or because the patient had been unattended by a physician. To this extent rheumatic heart disease is a problem of interest to students of forensic medicine. Only 4.0 per cent of deaths from subacute bacterial endocarditis were the subject of a coroner's investigation.

The mean annual death rate from rheumatic heart disease in hospitals among Jewish persons was approximately the same as among white gentiles.

Twenty-one deaths among hospital patients with rheumatic disease occurred during pregnancy and the puerperium; sixteen were directly attributable to rheumatic heart disease. Of 116 pregnant women with rheumatic heart disease 18.1 per cent died. This high percentage is probably due to the severity of their condition on admission and to the likelihood that some cases of rheumatic heart disease which survived pregnancy were not identified for study because of obsolete filing systems and diagnostic nomenclature in some maternity hospitals.

AUTHOR.

Clahr, Jacob, Klein, Milton D., and Greenstein, Nathan M.: *Rheumatic Heart Disease in Pregnant Women*. New York State J. Med. 40: 1242, 1940.

The establishment of the prenatal cardiac clinic has led to a threefold increase in the number of diagnosed cases of rheumatic heart disease in pregnancy.

The routine treatment of cases of rheumatic heart disease in pregnancy has been described.

The combination of adequate bed rest and digitalis has been the most effective means in the prevention of intra-partum and post-partum cardiac failure in rheumatic heart disease.

The only maternal deaths occurred in patients who had neither adequate bed rest nor digitalis.

AUTHORS.

Thacker, E. A.: *Blood Pressure Studies on University Students, Including the Effect of Exercise on Essential Hypertension, Hypotension, and Normal Subjects*. Ann. Int. Med. 14: 415, 1940.

Students were divided into high, normal, and low blood pressure groups, a careful history taken on each, and the blood pressure reactions to a standard exercise test were recorded.

The increase in the systolic blood pressure following exercise was greatest in the high blood pressure group.

The systolic pressure after exercise in the hypertensive and hypotensive classes returned to normal more slowly than did the normal group.

The diastolic pressure during exercise fell on the average about as far below the basal level as the diastolic rose above the basal level with the cold test. This pressure returned to the original level somewhat more slowly in the hypertensive group.

There was a far greater difference between the usual or regular systolic blood pressure and the basal blood pressure in the hypertensive class than between those levels in the normal and low pressure groups. This criterion is a definite aid in discovering those cases in which the blood pressure should be checked more frequently.

The pulse rate following exercise returned to the basal rate within two minutes in the normal and low pressure subjects.

Vasomotor response from other factors plays a more important role in causing a systolic increase in blood pressure during exercise than does the pulse rate.

The same factors which govern the emotional status of an individual play an important part in the blood pressure reaction.

There is a definite hereditary factor in the regulation of blood pressure. The tendency toward essential high or low blood pressure is carried by the germ plasma from one generation to the next.

The amount of work or exercise apparently is not an etiologic factor in the production of essential hypertensive blood pressure.

The quantity of food intake may be an etiologic factor in producing high blood pressure, since there were two and one-half times as many heavy consumers of food in this class as in either of the other groups.

At least two or three subsequent rechecks should be made before a person is classified into the hypertensive or hypotensive group. This will prevent worry and anxiety in certain patients, and will be of considerable value to the physician in arriving at a correct diagnosis.

AUTHOR.

**Sperling, Louis: Aneurysm of the Splenic Artery. Surgery 8: 633, 1940.**

A calcified aneurysm of the splenic artery is reported. The classical roentgenologic picture described by Lindboe was present and led to a correct preoperative diagnosis. The aneurysm was excised, together with the spleen, and the patient made an uneventful recovery. This is the twelfth recorded instance in which the patient recovered from operation for aneurysm of the splenic artery. Seven additional cases recorded in the autopsy material (33,810 autopsies) of the Department of Pathology of the University of Minnesota are added to those previously reported in the literature.

AUTHOR.

**Gross, Louis: The Cardiac Lesions in Libman-Sacks Disease. With a Consideration of Its Relationship to Acute Diffuse Lupus Erythematosus. Am. J. Path. 16: 375, 1940.**

A study has been made of the hearts from twenty-three fatal cases of disseminated lupus erythematosus. The lesions observed were compared with the cardiac lesions in four cases of "atypical verrucous endocarditis" without lupus erythematosus. The characteristic macroscopic valvular and mural endocardial lesions of "atypical verrucous endocarditis" were observed in at least eight cases of lupus erythematosus. Moreover, microscopic lesions were observed in all of the twenty-three cases, particularly in the valve rings, valve leaflets, valve pockets, mural endocardium and pericardium. With few exceptions, these lesions were characteristic of the disease and many were identical with those observed in the four cases without lupus erythematosus.

In a discussion of terminology, it was pointed out that the pathologic lesions were not confined to the heart and might involve other organs, particularly the vessels of the kidney. On the other hand, these vascular lesions in other organs are sometimes mild and occasionally absent. Furthermore, it is possible that the clinical syndrome may occur without demonstrable cardiac lesions, although macroscopic or microscopic lacerations were invariably present in this series. The common denominator appears to be the clinical features described by Libman and Sacks, the cutaneous manifestations of diffuse lupus erythematosus being frequently but not invariably present. It is, therefore, suggested that the two groups of cases which have been previously called acute disseminated lupus erythematosus and atypical verrucous endocarditis, respectively, should be placed into the single category of Libman-Sacks disease.

Criteria are described for the pathologic diagnosis of Libman-Sacks disease on the basis of cardiac lesions, and these are distinguished from the lesions of rheumatic fever and subacute bacterial endocarditis.

AUTHOR.

**Lewis, Thomas: The Adjustment of Bloodflow to the Affected Limb in Arteriovenous Fistula. Clin. Sc. 4: 277, 1940.**

Cases of arteriovenous fistula of the limbs are described in which the circulation to the distal part of the limb becomes restored to, or actually beyond, normal.

This compensatory increase appears to develop gradually over a period of years. It may be due in part to decreased vasomotor tone, but may also be due to vascular growth.

The growth of the distal arterial supply in arteriovenous fistula is of great interest from the general standpoint of collateral circulations. The idea that this growth may be explained simply by altered pressures or altered bloodflow, such as follow in the affected vessels as an immediate consequence of the original arterial lesion, cannot be supported. It is suggested that the growth is controlled by a stimulant, a chemical stimulant, arising locally as a product of the tissue need and acting locally.

AUTHOR.

Hines, Edgar A., Jr., and Barker, Nelson W.: Arteriosclerosis Obliterans. A Clinical and Pathologic Study. *Am. J. Med. Sc.* 200: 717, 1940.

A clinical study has been made of 280 consecutive cases of arteriosclerosis obliterans which were observed at the clinic. The clinical data have been supplemented by detailed gross and histologic studies of the arteries obtained from thirty-two legs that were amputated because patients had arteriosclerosis obliterans. The disease was found to occur predominantly among men between the ages of 50 and 70 years. There was no significant difference in racial incidence. The possible role of certain metabolic and chemical disturbances as etiologic factors has been emphasized. The lesions found in the arteries which were examined for pathologic changes consisted essentially of three components: 1. atheromatous plaques in the sub-intimal tissue, 2. degenerative changes in the medial coat, and 3. thrombosis. No significant difference was noted in the lesions of arteriosclerosis obliterans among diabetic and nondiabetic patients. The diagnosis and treatment are discussed in detail.

AUTHORS.

Katz, L. N., Sanders, A., Megibow, R. S., and Carlen, S.: Heart Size and Experimental Atheromatosis in the Rabbit. *Am. J. Med. Sc.* 200: 731, 1940.

The relationship of cardiac hypertrophy to coronary sclerosis was made the subject of direct experimental study.

For this purpose twenty-two rabbits were fed on a high cholesterol diet with the addition of the vitamin B complex. Sixteen of these rabbits subsequently developed moderate to severe atherosclerosis including involvement of the coronary arteries. The resulting heart weights of these were compared with eighteen rabbits serving as untreated controls and with 6 rabbits, which, although on the special diet, failed to develop gross or microscopic evidence of coronary or aortic atherosclerosis. All the rabbits were in the same age group with comparable body weights and the comparisons are therefore valid.

It was found that of the sixteen rabbits developing atherosclerosis twelve showed heart weights of more than 5 Gm. with an average cardiac weight of 6.3 Gm.; whereas the eighteen untreated control rabbits showed an average heart weight of 3.8 Gm., with only two hearts weighing more than 5 Gm.; while in the remaining six rabbits on the special diet but which did not develop atherosclerosis, only one heart weighed more than 5 Gm., and the average heart weight was 3.9 Gm.

To rule out factors other than the atheromatosis, direct systemic arterial blood pressures and pulse wave contours were obtained, and histologic sections carefully studied.

Evidence is presented to exclude atherosclerosis of the aorta, systemic arterial hypertension, aortic valvular defects, inflammatory disease of the myocardium, and other actions of the diet as factors in the production of cardiac hypertrophy in our experiments.

It is therefore concluded that coronary atherosclerosis per se produces cardiac hypertrophy in the rabbit. Ischemia of the heart appears to be involved in some way in the mechanism.

AUTHORS.

**Burstein, Charles L., Marangoni, Bruno A., DeGraff, Arthur C. and Rovenstine, E. A.:** Laboratory Studies on the Prophylaxis and Treatment of Ventricular Fibrillation Induced by Epinephrine During Cyclopropane Anesthesia. *Anesthesiology* 1: 167, 1940.

Ventricular fibrillation may be inaugurated in the dog by injecting small doses of epinephrine (0.01 mg. per kilo) during cyclopropane anesthesia.

Procaine, and the related chemical compounds studied: p-amino benzoic acid, the calcium double salt of benzyl succinic and p-amino benzoic acids, sodium p-amino benzoate, when administered before epinephrine, protected from this type of ventricular fibrillation.

Procaine administered intravenously, when ventricular tachycardia followed the injection of epinephrine, arrested the progression to ventricular fibrillation, and recovery to normal occurred after a shifting of the pacemaker to the auricles and finally to the sinus node.

The intracardiac injection of procaine was found to be efficient in the treatment of 66 per cent of animals having developed ventricular fibrillation following epinephrine injection during cyclopropane anesthesia.

AUTHORS.

**Good, Rankine:** Convulsive Cardiazol Therapy in Cardiovascular Disorders. *Brit. M. J.* 2: 624, 1940.

The main purpose of this paper is to demonstrate that cardiovascular disorders of even a severe degree—provided they are well compensated, and whether existing alone or in the presence of advancing years and of diseases of other systems—are not contraindications to the employment of convulsive therapy. Further, electrocardiographic examination in these cases provides no criteria indicative of how well or how badly the patient will stand up to the convulsion.

AUTHOR.

**Hoffmann, Martin H., Sandler, Nathaniel, and Hecht, Hans:** Paroxysmal Auricular Fibrillation Complicating Metrazol Shock Therapy. *Am. J. Psychiatry* 97: 372, 1940.

A case of paroxysmal auricular fibrillation is presented. The arrhythmia persisted for five hours following the initial injection of metrazol which resulted in a strong epileptiform seizure. The various possible mechanisms are discussed and particular emphasis is laid upon the possibility of its "central" reflex origin.

AUTHORS.



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\*Executive Committee.

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## Original Communications

### PHYSIOLOGIC AND PHYSICAL LAWS THAT GOVERN AUSCULTATION, AND THEIR CLINICAL APPLICATION

#### THE ACOUSTIC STETHOSCOPE AND THE ELECTRICAL AMPLIFYING STETHOSCOPE AND STETHIOGRAPH

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BOSTON, MASS.

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I. INTRODUCTION

THE stethoscope is over 120 years old. It has withstood the criticisms of the earlier decades of its life, and its position as a diagnostic instrument is secure. The physical and acoustic principles of this instrument, however, have been imperfectly understood, and insufficient investigation has been undertaken in the analysis of the various stethoscope forms. In most instances, when such study has been attempted, the chest piece has been used as a sound collector of controlled vibrations in open air, and not in its normal position against the chest wall. In a sense, it has been compared to an airplane detector rather than a submarine detector.

At the Cardiac Clinic of the Massachusetts General Hospital, since its foundation by Dr. Paul D. White, in 1914, the importance of using both the bell and diaphragm chest pieces in examination of the heart has been insisted upon. The clinical work of one of us (H. B. S.) led, in 1925, to the combining of the two chest pieces, connected by a valve, into a single instrument. Other methods of combining them had been previously devised, but were not familiar to the profession in this country. Although they are clinically valuable, the exact acoustics of such instruments have not been previously analyzed by modern electrical methods. The engineering and manufacturing experience of one of us (M. R.) made it possible to undertake such a study. The investigation was extended to include ideal stethoscope forms, the influence of tubing length and material on the binaural stethoscope, diaphragm thickness, a comparison of binaural with monaural effects, types of heart sounds and murmurs, and energy output of cardiac vibrations. The study of the acoustic or mechanical stethoscope led to a review of the advances in

electrical transmission and recording of vibratory phenomena over the heart, and to a description of a new instrument for accurate registration of these phenomena by simultaneous employment of the electrocardiograph, stethograph, and pulse wave recorder.

We felt that the present interest in the graphic analysis and recording of the vibrations produced by the heart indicated a need for a more fundamental approach to the subject. The auditory phenomena of the heart can be understood only by the application of certain general principles of acoustics. These principles have been much more clearly defined in recent years by the electrical study of the human ear and by the perfection of electrical amplification.

We wish to express our appreciation of the cooperation of the Sanborn Company of Cambridge in this investigation. We are also grateful for the constructive criticisms of Professor Hallowell Davis of the Harvard Medical School and Dr. Paul D. White of the Massachusetts General Hospital.

## II. HISTORY OF THE STETHOSCOPE

*Prestethoscope Era.*—Auscultation, a method of investigation of the functions and conditions of the respiratory, circulatory, digestive, and other organs by the sounds they themselves produce, or that are elicited by percussion, is one of the most ancient modes of diagnosis. From the classic passage in Hippocrates' work, "de Morbis," "If you listen by applying the ear to the chest," we have definite evidence that "immediate" auscultation was employed more than twenty centuries ago.

Harvey's dissertation, "de Motu Cordis," gives convincing information that the sounds of the heart had not escaped him; "it is easy to see when a horse drinks, that water is drawn in and passed through the stomach, with each gulp, the movement making a sound, and the pulsation may be heard and felt. So it is with each movement of the heart when a portion of the blood is transferred from the veins to the arteries, that a pulse is made which may be heard in the chest."

Corvisart made the following observation: "Some authors assert that they could hear, in certain diseases of the heart, the noise produced by the violent strokes of this organ, even at a small distance from the patient's bed. I have never had an opportunity, I repeat it, of ascertaining the unquestionably rare observations; I have barely heard these strokes by applying my ear close to the patient's thorax."

However, during the prestethoscope era physicians derived little benefit from auscultation other than that of sensing the pulsations of the heart by the mere application of the hand.

*The Laennec Stethoscope.*—"I was consulted," says Laennec (Traité de l'auscultation médiate, tome 1, p. 7), "in 1816 by a young woman

who presented some general symptoms of disease of the heart, in whose case the application of the hand and percussion gave but slight indications, on account of her corpulency. On account of the age and sex of the patient, the common modes of exploration being inapplicable, I was led to recollect a well known acoustic phenomenon, namely, if the ear be applied to one extremity of a beam, a person can, very distinctly, hear the scratching of a pin at the other end. I imagined this property of bodies might be made use of in the present case. I took a quire of paper which I rolled together as closely as possible, and applied one end to the precordial region; by placing my ear at the other end, I was agreeably surprised at hearing the pulsation of the heart much more clearly and distinctly than I had ever been able to do by the immediate application of the ear."

Laennec experimented further with his tube and finally evolved the instrument known as the "stethoscope."

"This consists simply of a cylinder of wood, a foot in length, perforated in its center longitudinally, by a bore three lines in diameter, and formed so as to come apart in the middle, for the benefit of being more easily carried. One extremity of the cylinder is hollowed out into the form of a funnel to the depth of an inch and a half, which cavity can be obliterated at pleasure, by a piece of wood so constructed as to fit it exactly, with the exception of the central bore which is continued throughout it, so as to render the instrument in all cases, a pervious tube. The complete instrument, that is, with the funnel-shaped plug infixed, is used in exploring the signs obtained through the medium of the voice and the action of the heart; the other modification, or with the stopper removed, is for examining the sounds communicated by respiration. A solid cylinder, without any perforation, is the best instrument for exploring the action of the heart; but as this form is not so good for examining the voice and respiration, the perforated cylinder is commonly used for all purposes."

Having developed a suitable stethoscope, Laennec undertook his epoch-making observations.

"I commenced immediately at the hospital Necker a course of observations, which have resulted in the discovery of new signs, sure, for the most part obvious, easy to be possessed of, and suitable to render the diagnosis of almost all diseases of the lungs, the pleuras, and the heart, more certain, and perhaps more circumstantial, than even the surgical diagnostic signs established by the aid of the probe or the finger." (*Traité de l'auscultation médiate*, tome 1, p. 8.)

*Piorry's Improvement.*—Piorry (1828) modified the Laennec stethoscope by reducing it to the thickness of a finger. He constructed an ear piece which overcame the difficulties experienced by some physicians

in obtaining a proper seal to the ear. Piorry's modification included a trumpet-shaped chest piece. Essentially, his instrument is the modern monaural stethoscope.

*The Binaural Stethoscope.*—The exact date of the first binaural stethoscope is unknown; several people have been credited with this invention. In 1907, C. T. Williams, in a paper in the *British Medical Journal*, described a stethoscope invented by his father (C. J. B. Williams) in 1829, and stated that it was probably the first binaural stethoscope ever made. In any event, Dr. C. J. B. Williams did describe a binaural stethoscope about 1843, and Dr. Arthur Leared demonstrated a binaural instrument in 1851. In Dr. Williams' early instrument, the tubes connecting the chest piece with the ear pieces were made of lead, and it was not until Dr. George P. Cammann first developed the binaural stethoscope with the flexible tubes that the true precursor of the present binaural stethoscope appeared. Cammann described his instrument in 1855. The chest pieces of all of these stethoscopes had a funnel or trumpet shape, with the acoustic characteristics of the so-called bell stethoscope. It was not until the invention of the diaphragm chest piece, with a rigid covering over the end of the collecting part, that a significant modification of the older bell type was developed. Dr. Marsh, of Cincinnati, in 1851, patented a stethoscope with a flexible membrane stretched over the end, but the phonendoscope devised by Bianchi, in 1894, and described also by Bazzi, in 1895, was the first instrument to have a rigid diaphragm. It was further modified by Baruch, of New York, in 1896. The chest piece of this type, which is in common use in this country at the present time, is the one patented by Dr. R. C. M. Bowles, of Brookline, Massachusetts, June 25, 1901. The importance of all these instruments rests in the fact that the rigid diaphragm acts to attenuate the low-pitched sounds and thereby accentuates the faint, high-pitched, blowing murmurs which are heard most characteristically in slight aortic regurgitation. Connor, in 1907, pointed out that this type of murmur can at times be heard best by applying the naked ear to the chest wall.

It would seem to be agreed at the present time that the bell chest piece and the diaphragm chest piece can satisfactorily cover the acoustic ranges necessary for clinical examination of the heart. However, the development of modern electric amplifying systems, with their freedom from background noise, has opened a new field for the graphic registration of heart sounds and murmurs, as well as respiratory sounds, which may well modify our clinical opinion in the future.

### III. CHARACTERISTICS OF THE HUMAN EAR IN AUSCULTATION

In auscultation, the human ear may be considered as the recording mechanism of an acoustic system, H. D. Arnold, in his introduction to

Harvey Fletcher's "Speech and Hearing,"<sup>2</sup> which is considered one of the best treatises on the subject from a physical standpoint, states:

"Our ears are only machines to translate air waves into a form suited to stimulate the auditory nerve; and as machines we may measure and describe them in the same terms that apply to devices we ourselves construct. We may compare them as to performance, and may accommodate our devices to their requirements. But, to understand the mechanism of the ear is by no means to understand the act of hearing, for we have not heard until the brain has perceived the message sent by the auditory nerve. We cannot explain in precise mechanical terms how this is done, nor indeed have we any clear comprehension of the process at present. Some important factors relating to the process of hearing we can, however, determine by measuring the least changes in sound which can be detected under a variety of conditions of pitch, loudness, and accompanying noise. Thus we may obtain a quantitative means of comparing individuals in this respect, and establish a standard of average hearing."

*Threshold of Hearing and Feeling vs. Frequency.*—Pure tones of different periods of oscillation or frequency, but of similar intensity, affect the human hearing mechanism to different degrees. Investigations which ascertained the actual intensity of sound at the threshold of audibility were made by Fletcher,<sup>2</sup> Toepler and Boltzmann,<sup>3</sup> Rayleigh,<sup>4</sup> Wead,<sup>5</sup> Wein,<sup>6</sup> Abraham,<sup>8</sup> and Kranz.<sup>9</sup> Wegel<sup>10</sup> investigated the intensity of sound at the threshold of feeling.

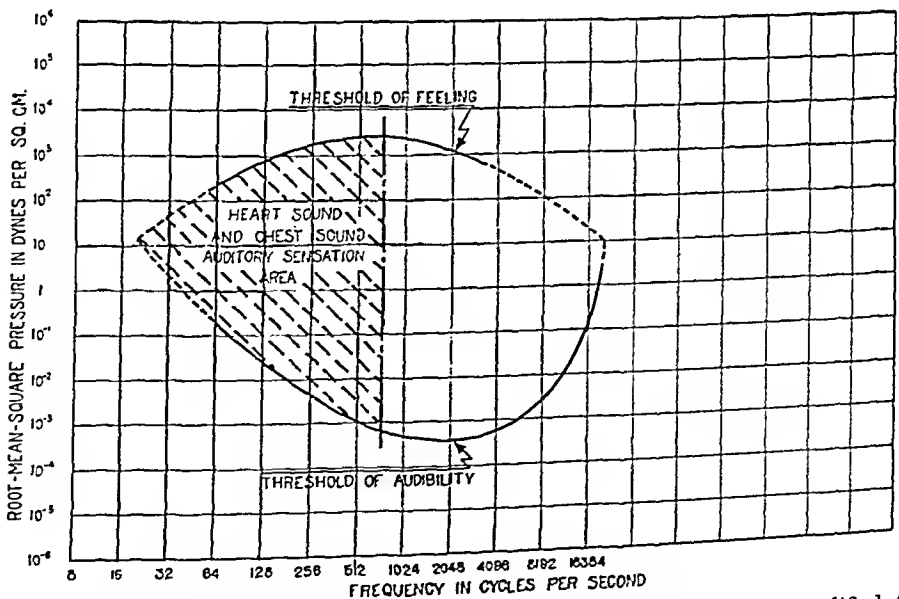


Fig. 1.—Average normal threshold curves of audibility and feeling (modified from Fletcher).

Fig. 1 shows the curves representing average thresholds of feeling and audibility which were obtained on a large number of persons by Fletcher. The threshold of audibility curve represents the pressure variations in dynes per square centimeter, or bars, which are necessary to produce a sound of minimum audibility between the frequency limits of approximately 20 and 20,000 cycles per second. The threshold of

feeling curve represents the pressure variations beyond which a sensation of pain is created. The area enclosed by the upper and lower curves represents the auditory sensation area. The threshold curves of any one person would not be so smooth (peaks and valleys are superimposed), for there are hardly two sets of ears that are identical. The broken portions of the feeling and audibility curves are obtained by extrapolation, which is made necessary by the fact that the phenomena are not clearly defined in these regions. The shaded area represents the auscultation region with which we are concerned.

*The Decibel.*—The human hearing mechanism is capable of functioning over an enormous range of sound pressure or sound energy variations. To express this property of hearing in quantitative terms of pressure or energy would require the use of numbers of such magnitude that their arithmetical manipulation and visualization would be impractical. The communications engineer was confronted with this problem and overcame it by employing the decibel system of measurement.

The bel is essentially a logarithmic unit, or the common logarithm of the ratio of two values of sound power, and the decibel, as the term indicates, is one-tenth of the bel. An approximate characteristic of hearing is that equal variations of sound intensity along a logarithmic or decibel scale approximate similarly equal variations of loudness as they are perceived by a normal human ear. Also, a one-decibel variation in power level of sound is approximately the minimum change that may be detected by the average human being.

In the decibel scale relative sound intensities are always expressed in terms of differences in decibels, never as a ratio of decibels or a percentage change in decibels. From the definition of the decibel, one decibel merely represents a sound pressure ratio equal to the twentieth root of 10, or a ratio of 1.12 to 1. That is, two sounds which differ by one decibel have their pressures in the ratio of 1.12 to 1. Similarly two sounds which differ by 20 decibels have their pressures in the ratio of the twentieth power of 1.12, or 10 to 1. If a sound pressure level is doubled, the change in decibels is twenty times the logarithm of 2, which is 6 decibels. Thus, doubling a given sound pressure always increases by 6 decibels the original level, no matter what the value of the original level was.

In order to obtain a better conception of the relative values in a decibel scale, let us consider Table I. In the application of the decibel scale to the measurement of the intensity of sound, a reference point, such as the threshold of hearing, is commonly employed. Table I lists the average decibel equivalents above the hearing threshold of various sources of noise. The instantaneous values may vary plus or minus 10 decibels from the values given. The first three columns were obtained in a survey by the New York City Noise Abatement Commission. The fourth column was added by us to illustrate the tremendous range in intensity that exists between the threshold of hearing and the threshold of pain. Column four is merely an expression of column three, converted into equivalent intensity ratios with the threshold of hearing as the reference value.



TABLE I

SOURCE OR DESCRIPTION OF NOISE	DISTANCE FROM SOURCE (FEET)	NOISE LEVEL (DECIBELS)	NOISE LEVEL (AMPLITUDE RATIOS)
Threshold of pain		130	3,162,000
Hammer blows on steel plate (al- most painful)	2	114	501,200
Riveter	35	97	70,790
Elevated train	15-20	90	31,620
Average motor truck	15-20	75	5,620
Busy street traffic	15-75	68	2,512
Average automobile	15-50	66	1,995
Ordinary conversation	3	65	1,778
Rather quiet street (residential)	15-300	58	794.0
Quiet automobile	15-50	50	316.2
Average office		47	223.9
Noisy residence		45	177.8
Very quiet radio in home		40	100.0
Average residence		32	39.8
Average whisper	4	20	10.0
Rustle of leaves in gentle breeze		10	3.1
Threshold of hearing		0	1.0

*Minimum Perceptible Changes in Intensity and Frequency.*—A law in psychology, known as the Weber-Fechner law, states that the stimulus increase required to produce a discernible sensation increase maintains a ratio which is constant to the total stimulus. Another way of stating the Weber-Fechner law is that the magnitude of the produced sensation is proportional to the logarithm of the stimulus. When the Weber-Fechner law is applied to hearing, it may be stated that a barely perceptible increase in sound intensity, as detected by the human ear, should exhibit itself as a constant which is independent of the sound intensity.

Knudsen<sup>11</sup> is to be credited with the first accurate determination of the minimum perceptible variations in intensity between the frequency limits of 100 and 4,000 cycles per second. Fletcher,<sup>2</sup> by a modification of the testing procedure, extended the frequency band between the limits of 35 and 10,000 cycles per second. Knudsen and Fletcher observed some variation in the Weber-Fechner law, as applied to hearing, in that the average ear was most sensitive to variations in intensity at sensation levels above 50 decibels, and particularly did this hold true in the middle of the frequency band. An intensity variation of 5 to 10 per cent was detectable for sound levels above 50 decibels at approximately 2,000 cycles per second. At the lower sound levels, and more so at the extreme ends of the frequency band, a decidedly greater percentage variation in intensity was required to produce a perceptible change. As a comparative illustration, it was found that a 70 per cent variation in intensity was necessary at 2,000 cycles per second in order to produce the minimum perceptible change when the sound level was down to 10 decibels.

In auscultation, this characteristic of human hearing is an extremely important factor, in that the intensity level is most often 10 decibels, or less, in addition to the fact that the frequency band which is involved is at the lower extreme. As an illustration, at a frequency of 60 cycles per second a variation of 20 per cent is just perceptible when the sound level is 50 decibels, and a variation of as much as 200 to 300 per cent is necessary at the intensity level of 10 decibels.

The human ear is a far better detector of changes in frequency than it is of changes in intensity. Shower and Biddulph,<sup>12</sup> as well as Knudsen, have made extensive investigations in order to ascertain the minimum perceptible frequency changes at the various sensation levels. They found that a higher sensation level of sound required less of a frequency change for minimum perceptibility. Also, the ear was found to be less sensitive to frequency variations as the lower end of the frequency band was approached. Between 500 and 4,000 cycles per second, the minimum perceptible fractional difference in frequency is 0.3 per cent at a sensation level of 40 decibels. At 64 cycles per second the minimum perceptible fractional difference in frequency is of the order of 1.1 per cent; at 128 cycles per second it is 0.6 per cent; and at 256 cycles per second it is 0.4 per cent.

*Minimum Tonal Perception Time.*—Another important measurement pertaining to auscultation is the minimum amount of time required for a tone to excite the hearing mechanism. Stewart's<sup>13</sup> uncertainty principle states that the ability of the ear to recognize a tone of brief duration decreases as the duration decreases. Stewart expressed his principle mathematically by saying that the product of the duration of the tone by the number of cycles of uncertainty in ascertaining the pitch of the signal is equal to unity. It naturally follows from this expression that, in the lower frequency band, such as is encountered in auscultation, the frequency may be varied rapidly over a considerable portion of an octave without detection by the ear. This phenomenon may be illustrated if a vibrato with a frequency of 60 cycles per second is varied by two semitones at a rate of seven times per second; the variation cannot be detected by the ear. Table II (after Fletcher) presents some probable values as regards tonal perception.

TABLE II

FREQUENCY	WEAK TONES		MEDIUM TONES	
	TIME (SECONDS)	CYCLES	TIME (SECONDS)	CYCLES
128	0.0946	12.1		
256			0.06908	17.6
384	0.0627	24.08	0.0445	17.1
512	0.0579	29.64	0.04274	21.8

*Masking Effects.*—Everyone has noted that in a rather noisy location he unconsciously increases the intensity of his voice in order to make

himself heard. The reduction in the ability of the ear to detect certain sounds in the presence of other sounds is technically known as masking. Mayer,<sup>14</sup> in 1876, was one of the first to show experimentally that low-pitched sounds had a masking effect which differed from that produced by high-pitched sounds. Mayer claimed that a low-pitched tone was capable of completely masking a tone of higher pitch, but that a higher pitched tone was incapable of completely masking the lower pitched one. The equipment used by Mayer in his experiments was rather crude, so that the accuracy of his work was limited. The Bell Telephone engineers continued the study and obtained accurate data which were published in Fletcher's "Speech and Hearing."

Experimenters in the Bell Telephone Laboratories found that Mayer's conclusion on masking holds true only under certain conditions. A low-pitched tone will not mask to any degree a high-pitched tone far removed in frequency unless the low-pitched tone is of a very considerable intensity; a higher pitched tone may easily mask a lower pitched tone if the frequencies are closely spaced.

In a complex tone, as, for example, one consisting of three frequencies, such as 300, 400, and 2,000 cycles per second, with respective sensation levels of 50, 10, and 10 decibels, the experimenters found that the average human ear could detect only the 400- and 2,000-cycle tones. When the intensity of each component of the complex sound was increased by 30 decibels, so that the resulting three tone levels were 80, 40, and 40 decibels, respectively, it was noted that the 300- and 400-cycle tones were the only ones audible. Under these conditions, when the 300-cycle tone was attenuated by only 8 decibels, it vanished completely. From this example it follows that the sensation produced on the ear by a complex sound is decidedly different in character, as well as in intensity, when the level is decreased or increased, even though no distortion is introduced. *This peculiar characteristic of hearing follows the general rule that, as a complex sound becomes more intense, the low-pitched tones will become more prominent because of the fact that the higher pitched tones are masked.*

When a radio receiver is tuned to a station which is broadcasting a symphony, this masking effect will readily become apparent if one listens first at high volume, and then turns the volume control to a much lower level. At the high volume setting the bass notes come through with excellent fidelity, but at the low volume setting a decided attenuation in the bass will immediately become apparent.

In auscultation this masking effect is even more noticeable because of the proximity of the frequency components which are involved. It follows that obesity should have an attenuating effect and produce a decided change in the quality of the heart sounds. Furthermore, some of the important components of the heart sounds might be completely masked by obesity.

Another type of masking effect is introduced, especially in auscultation, when a sound of comparatively large volume immediately precedes a sound of considerably less volume, as, for example, when a first or second heart sound precedes a murmur of low intensity. The first or second sound of comparatively great intensity has a tendency temporarily to fatigue the ear, thereby masking the low intensity murmur. The diaphragm type of stethoscope chest piece partially overcomes the masking effect by selective attenuation, the principle of which will be discussed later.

*Frequency Response Characteristic.*—Because of the fact that the human ear does not respond equally to different pitches, tones of the same intensity but of different frequencies produce different sensations of loudness. Also, if the intensities of the tones of different pitch but of equal loudness are increased by an equal amount, an unequal sensation of loudness is produced. Kingsbury<sup>15</sup> and, more recently, Fletcher and Munson<sup>16</sup> obtained quantitative measurements on the determination of equal loudness curves for average subjects.

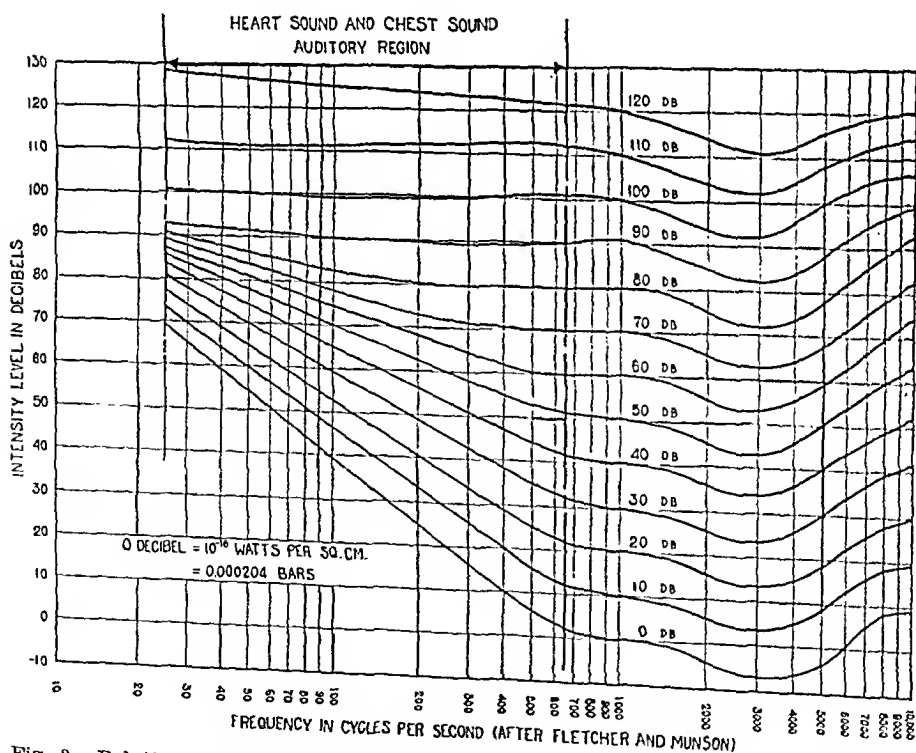


Fig. 2.—Relative sensitivity curves of the average normal human hearing mechanism.

Fig. 2 shows the curves obtained by Fletcher and Munson. The abscissas of the graph, which is a logarithmic scale, represent the frequency band in cycles per second that is covered by the average human ear, and the ordinates are the intensity levels, applied to the ear, in decibels. The family of curves was obtained for equal steps of increase in intensity (indicated on each curve in decibels) above zero decibels,

which represent the threshold level and are equivalent to  $\frac{1}{10,000,000,000,000,000}$  or  $10^{-16}$  watts per square centimeter of sound excitation on the ear, or 0.000204 bars.

From the family of curves, it may be seen that the maximum sensitivity of the average ear is in the vicinity of 3,000 cycles per second. In the frequency band above 1,000 cycles per second, a given increase in the intensity level results in approximately the same increase in loudness, whereas in the very high, and, more so, in the low frequency regions, lesser increases in intensity produce a greater sensation of loudness. Resolving this statement into actual values from Fig. 2, at a frequency of 600 cycles per second an increase in intensity of 76 decibels is necessary to create a loudness level of 80 decibels above the threshold level of zero decibels, whereas, at 100 cycles per second, an increase of about 43 decibels is necessary to produce an equal increase; at 8,000 cycles per second, 80 decibels are required, and, at 1,000 cycles per second, 80 decibels. It is very important that this nonlinear characteristic of the ear be taken into consideration when designing a stethoscope, for a modification of the frequency response characteristic of the stethoscope will seem to alter the quality of the heart and chest sounds.

#### IV. DESCRIPTION OF HEART SOUNDS, MURMURS, AND NONCARDIAC CHEST SOUNDS FROM A PHYSICAL POINT OF VIEW

*Transmissional Characteristics.*—Acoustics, as related to auscultation, deals with the vibrations or disturbances set up in the chest and their transmission through the component sections of the chest, as well as through the stethoscope, and with the resulting effects on the observer's ear. Sound, which is the result of vibration of a medium, is capable of traveling through a solid, liquid, or gas as a compressional wave, unless the medium is entirely inelastic. In other words, the ability of sound to travel through matter depends upon the elasticity, viscosity, and density of the medium. If the effects of viscosity are small, as is the case with water, air, metal, and bone, the sound energy may be transmitted with little loss. In some media, such as soft rubber or fatty breast tissue, the sound waves are almost immediately suppressed.

In a homogeneous substance a sound wave will propagate itself at a velocity whose magnitude depends on the physical properties of the medium, and the attenuation of the wave will be governed by the viscosity and the spreading of the sound energy over a larger surface as the wave progresses. When sound energy travels from one medium into another of different physical properties, or when there is no longer homogeneity of medium, transmission losses in the form of refraction and reflection take place. Some media are capable of transmitting low frequency vibrations with less attenuation than high frequencies, and vice versa; this results in a distortion of the sound.

There are many paths along which heart and chest sounds travel in the human body in order to reach the surface. A large percentage of the sound energy never reaches the surface because of viscosity, elasticity, density, spreading, reflection, and refraction losses. Naturally, the intensity of the sound is maximum over the portion of the chest where

the sound pursues a path of minimum attenuation, and this location the physician normally selects with his stethoscope. Auscultatory experience has definitely shown that murmurs produced by lesions of the four valves of the heart are heard with maximum intensity in certain areas of the chest, although there may be other sections of the chest surface which are closer to the valves under observation.

*Classification of Sounds.*—Trendelenburg,<sup>17</sup> Williams and Dodge,<sup>18</sup> Pierach,<sup>20</sup> Landes,<sup>21</sup> and Cabot and Dodge<sup>22</sup> have attempted to ascertain what frequency band is involved in auscultation. Cabot and Dodge<sup>22</sup> came to the following conclusions:

“Practically all the sounds of interest in auscultation are made up of frequencies below 1,000 cycles per second. In general, the upper and lower frequency limits for the pathologic sounds in any particular case are not sharply defined.

“Presystolic murmurs as a class are characterized by a greater predominance of low frequencies than other murmurs, and are almost invariably termed low pitched.

“The frequency bands of importance in systolic and diastolic murmurs are broadly the same. In each group, extremely low-pitched and high-pitched cases are found, but there appears to be nothing in the quality of the sounds that is characteristic of murmurs occurring in systole or diastole. In our limited studies, we have not been able to associate a particular frequency band with murmurs produced by a lesion of a given kind.

“Lung sounds, as a class, have a proportionately smaller amount of low frequency components than heart sounds. The descriptive words ‘coarse’ and ‘fine,’ as applied to râles, are usually associated with conspicuous ‘low’ and ‘high’ frequency components. Breath sounds are, broadly, higher pitched than most heart sounds, as evidenced by the scarcity of components below 240 cycles per second.”

Williams and Dodge<sup>18</sup> observed the distribution of energy in the normal heart sounds as given in Table III.

TABLE III

FREQUENCY (CYCLES PER SECOND)	ENERGY (PER CENT)
50-60	56
60-70	27
70-80	10
80-90	4
90-100	2
100-110	1

Above 110 cycles per second, the energy components of the normal heart sounds were found to be negligible. Williams and Dodge further observed that low-pitched heart murmurs are composed of frequency components below 400 cycles per second and that high-pitched murmurs range from 120 to 660 cycles per second. Systolic and diastolic murmurs are composed principally of energy components between 120 and 660 cycles per second, occasionally ascending to 1,000 cycles per second. Cabot and Dodge<sup>22</sup> noted that the frequency of presystolic murmurs lies,

for the most part, below 140 cycles per second, but they may contain components up to 400 cycles per second. They stated that the pericardial rub is composed of frequencies between 140 and 660 cycles per second, that râles lie between 120 and 1,000 cycles per second, amphoric breathing between 240 and 660 cycles per second, and bronchial breathing between 240 and 1,000 cycles per second.

In our observations on the frequency components of the various heart sounds and murmurs, we have not encountered any of noticeable value above 650 cycles per second. We have, however, encountered frequency components of murmurs and heart sounds that were well below the range of the human ear (obtained by recording the sounds graphically). Just where the lower limit of the sounds actually occurred was rather difficult to observe accurately, for they were intermingled with the low frequency chest wall motions. The lowest frequency limit of heart sound and murmur components is in the vicinity of 5 to 10 cycles per second, although sounds with a frequency of less than 30 to 40 cycles per second cannot be heard if the intensity is low.

#### V. THE ACOUSTIC STETHOSCOPE

*General Classification.*—The acoustic stethoscopes may be classified as monaural, binaural, and differential. The monaural stethoscope described earlier in this paper was invented by Laennec and later improved by Piorry. It is still in use on the continent of Europe, but the binaural stethoscope is more commonly used. There are many kinds of binaural stethoscopes, but the only two really important types are those with open and diaphragm chest pieces.

The differential stethoscopes are primarily instruments for localizing and comparing sounds. Their operation depends on the well-known characteristic of hearing termed "auditory localization," or the ability to ascertain the direction of a sound source by means of phase differences. Phase difference depends on when the sound reaches each ear, and, in turn, registers on the brain. In addition, there is a stereophonic effect which gives the sound characteristic depth and extensiveness.

Alison,<sup>58</sup> in 1859, described a differential stethoscope which consisted of two monaural stethoscopes of the flexible-tube type. Muralt,<sup>59</sup> in 1910, devised a differential stethoscope which allowed him to listen simultaneously to two lung areas. Muralt's stethoscope incorporated two similar chest pieces, so arranged that two tubes of equal length connected each chest piece with each ear; four tubes were used in all. In 1934, Fröschels<sup>60</sup> suggested using a differential stethoscope to study the sounds produced by the vocal cords in order to detect laryngeal paralysis. Fröschels' stethoscope was a modification of Muralt's, in that it consisted of two similar chest pieces and two tubes passing through an X which allowed an *ipso-* or *contralateral* course of sound to each ear. Hawthorne,<sup>61</sup> in 1935, described a differential (double) stethoscope which was similar to Alison's. In 1936, Nicolai<sup>62</sup> described what he termed a "Stereostethoscope," to detect differences in sounds originating in the two mandibular joints. The Nicolai "Stereostethoscope" was identical with the one described by Alison. Nicolai and Hantschmann<sup>63</sup> found the Nicolai "Stereostethoscope" useful in the study of pulmonary and cardiac disease.

Kerr, Althausen, Bassett, and Goldman,<sup>85</sup> of the University of California Medical School, described another instrument which they called the "symballophone" and classified it as a "modified stethoscope for the lateralization and comparison of sounds." The "symballophone" is similar to Muralt's stethoscope, except that a longer connecting tube from each chest piece to the opposite ear piece is employed in place of the direct tube to the ear piece on each side.

Many variations and styles of bells have been manufactured and marketed with wide claims for their performance, but rarely has a theoretical or scientific explanation of the acoustics of the bell been attempted. Similarly, the acoustics of the stethoscope structure between the bell and the ear has been ignored. With due credit to the contribution of medical men to the development of the stethoscope, the fact cannot be overlooked that this commonly used instrument is lacking in certain elements of scientific design.

*Principle of Operation.*—The stethoscope is a device which provides a closed acoustic system for conducting the sounds that originate in the body of the patient to the observer's ear. The sound transmission medium is a closed column of air in the case of the binaural stethoscope, which employs rubber tubing as a link between the bell, or sound accumulator, and the ear pieces. In the rigid monaural stethoscope, the sound travels by both bone conduction and air column transmission. The bone conduction is dependent upon contact with the ear as well as with the material of which the stethoscope is made, whereas transmission by air column depends upon the pressure changes that take place.

*The Open Bell.*—In medical literature the limited references to attempts to analyze the acoustics of the bell portion of the stethoscope show that the unit is regarded merely as an accumulator or collector of sounds. The general trend of thought has been that, if the sound as it accumulates on a patient's chest could be gathered from the largest practical area, there would be a proportional increase in intensity when it is transmitted to the ear (Barss, Eade, and Fitzgerald,<sup>86</sup> Tobler<sup>87</sup>). According to this reasoning, the larger the diameter of the contact area of the bell consistent with good seating, the greater the heart sound intensity. Limited clinical trial seemed to substantiate this supposition. Various types of bells whose construction was based upon these assumptions have been marketed. Other designers went a step further by giving the internal portion of the bell various geometrical shapes in order to aid the accumulating properties.

It is our opinion that the open bell should not be considered primarily as an accumulator. When it is held in the open, the open bell exhibits acoustic characteristics that are entirely different from those which it exhibits when it is applied to the chest. *When an open bell is applied to the chest, the skin bounded by the lip of the bell forms a diaphragm, and the fleshy portion under the skin acts as a damping medium.* In other words, the condition is somewhat similar to that encountered in a microphone or telephone receiver.



The physical principles governing the operation of a damped diaphragm are well known and may be found in textbooks on telephony. Any diaphragm has a natural period of vibration, or resonance point, which is dependent upon its inherent inertia, elasticity, diameter, and tautness. The maximum sensitivity of the diaphragm to external excitation occurs at the point of resonance. In other words, if a diaphragm (made of any material) is excited by sound or vibrational energy whose pitch or frequency is varied from zero to infinity while the amplitude is kept constant, the diaphragm will oscillate in unison with the exciting medium and reach a maximum oscillation amplitude at its point of resonance. The following are some of the general rules governing the action of diaphragms:

A. The more taut a diaphragm is drawn, the higher does its natural period of oscillation become.

B. The larger the diameter of the diaphragm, the lower will be its natural period.

C. Damping serves the purpose of suppressing the maximum vibrations of the diaphragm that occur at the resonance point.

D. When the natural period of a diaphragm is increased, the upper frequency range to which the diaphragm is capable of responding is increased. This effect cannot be attained, however, without lowering the sensitivity of the diaphragm throughout its entire frequency range. Thus, a diaphragm with a higher natural period is less sensitive to the lower frequencies or pitches than a diaphragm of lower natural period.

E. Diaphragms have harmonic resonance points which occur at multiple frequencies of the fundamental. In auscultation, we are concerned only with the fundamental.

F. At the frequency of mechanical resonance of the diaphragm the effects of the inertia and elasticity of the diaphragm balance each other, and its velocity is in phase with the impelling force.

If we regard the open bell of the stethoscope as a device for producing a diaphragm effect when it is applied to a patient's chest and keep in mind the physical characteristics of diaphragms, many clinical observations become explainable. It is a commonly observed fact in auscultation that, for a bell of a given size, the greater the pressure with which the bell is applied to the patient's chest, the less the apparent intensity of the first and second heart sounds and the higher the pitch. This phenomenon is readily explained by the fact that, with greater pressure, the skin bounded by the lip of the bell is drawn more taut; this produces a diaphragm with a higher natural period than when the pressure is light. As has been said, a diaphragm with a high natural period extends the upper portion of the frequency band, but, at the same time, attenuates the over-all level except at the point of resonance. It is to be expected that a diaphragm with a high natural period would attenuate the lower frequency components of the heart sounds and tend to bring out the higher frequency components, thereby altering the pitch and reducing the intensity of the first and second heart sounds, in which the low frequencies predominate.

It is noted normally that the smaller the diameter of the opening of the bell, the higher the pitch of the sounds. This characteristic is ex-

plained by the fact that, with a small bell, the diaphragm dimensions are small, and this tends to give it a higher natural period. Also, in order to obtain a reasonably good seal with the skin, sufficient pressure is exerted to stretch the skin enclosed by the lip of the bell, thereby additionally raising the natural period. With a bell of larger diameter, the tendency to stretch the skin is proportionally reduced; this makes a stethoscope with a bell of large diameter insensitive to pressure variations as regards pitch, whereas a stethoscope with a small bell is very susceptible.

The pressure-pitch characteristic of stethoscopes has a useful application in auscultation when a bell of normal size (about one inch in diameter) is employed. By varying the pressure on the patient's chest, the physician creates a variable filtering action upon the heart sounds that are transmitted by the closed system. In order to clarify the principle, let us consider a pathologic condition in which there are normally loud first and second heart sounds, a loud systolic murmur of fairly low pitch, and a very low intensity, hardly audible, high-pitched diastolic murmur. Because of the comparatively great intensity of the sounds other than the diastolic murmur, the latter is masked (as explained under *Masking Effects*). When the pressure with which the stethoscope is applied is increased, the natural period of the diaphragm formed by the skin is raised, thereby attenuating the lower pitched components, of which the first and second heart sounds, as well as the systolic murmur, are composed, and allowing the higher pitched diastolic murmur to stand out better as a result of the decreased masking effect. When the pressure with the stethoscope is decreased, low-pitched murmurs, third heart sounds, and gallop rhythms may be brought out more distinctly.

Another very important consideration in regard to the open bell is the effect of its internal dimensions and shape. As has been previously mentioned, various geometrical shapes and forms were devised to improve the accumulating properties of the open bell, with a resulting loss of accumulation in most cases. The fallacy in making bells of certain geometrical shapes becomes obvious if we consider the stethoscope from the point of view that the pressure variations at the ear which are produced by the skin diaphragm in the stethoscope proper are inversely proportional to the volume of the bell. Thus, an infinitely small volume produces a maximum variation in pressure, which, in turn, manifests itself as a sound of maximum intensity. The only important consideration in designing a bell, aside from keeping the internal volume at a minimum, is to have it so shaped that, in the case of an obese patient, the bell will not fill with flesh to such an extent as to decrease the diameter of the diaphragm and, therefore, its effect.

At this point it is logical to consider the relationship of bell resonance to dimensions. A stethoscope bell may be placed in the same class as the Helmholtz resonators, an analysis of which may be found in almost any text on acoustics. Although it is somewhat beyond the scope of this paper to go into the acoustics of

Helmholz resonators as applied to stethoscope bells, it is of interest to note that a bell with an internal lip diameter of 5.8 cm. and an internal body depth of 0.9 cm., with a 0.6 cm. hole, 1 cm. long, through the threaded portion (which attaches to the stethoscope proper), has a theoretical resonance frequency of approximately 500 cycles per second. Because of the fact that so large a bell has a resonance frequency which lies at about the upper limits of heart and chest sound frequencies, and bells of smaller size exhibit proportionally higher resonance frequencies, it is impossible to obtain any really effective filtering by bell shape modifications other than those previously mentioned.

*The Diaphragm Chest Piece.*—The diaphragm chest piece (Bowles type), which is commonly employed in auscultation, is especially useful in detecting faint, high-pitched sounds, such as the barely audible, high-pitched, diastolic murmur of aortic insufficiency and the high-pitched "bronchial" respiratory sounds. Essentially, the principle of its operation is similar to that of the open bell when it is applied to the patient's chest, except that additional attenuation of the lower pitched heart and chest sound components is obtainable. Of course, the smaller the diameter of the open bell, and the greater the pressure with which the bell is applied, the greater the low frequency attenuation, but, to obtain an equivalent degree of attenuation with the open bell, the pressure would be great enough to hurt the patient. By interposing a diaphragm of bakelite, or any other plastic whose natural period is in the desired range, the necessary attenuation is obtainable with light pressure on the patient's chest. In other words, the plastic diaphragm becomes a substitute for the skin diaphragm, and the flesh of the chest acts as a damping medium.

All of the general principles which are applicable to the skin diaphragm apply equally well to the plastic diaphragm. It is well to mention at this time that the plastic diaphragm is referred to because it is the one most generally employed. The theory of operation of a metal diaphragm is identical, but a foreign, metallic ring may be superimposed upon the sounds.

As is the case with the open bell, for maximum efficiency the volume of air in the diaphragm chest piece should be as small as possible. The internal volume of a diaphragm bell may be considerably less than that of an open bell of similar diameter, for the stiff diaphragm prevents the tissue of the patient's chest from entering and decreasing the effective diameter.

*Open Bell vs. Diaphragm Bell.*—An attempt was made to verify experimentally the theory of the stethoscope bell which has been discussed. A frequency characteristic run was made with the four bells shown in Fig. 3. Fig. 4 is a schematic sketch of the apparatus employed in the experiment.

The posterior portion of the patient's chest was allowed to rest against the loud-speaker, with its associated baffle. Throughout the entire test the patient was kept in one position relative to the loud-speaker. The four bells of Fig. 3 (the bells may be screwed into the specially designed microphone, the characteristics of which will be discussed later) were placed one at a time on an area marked on the

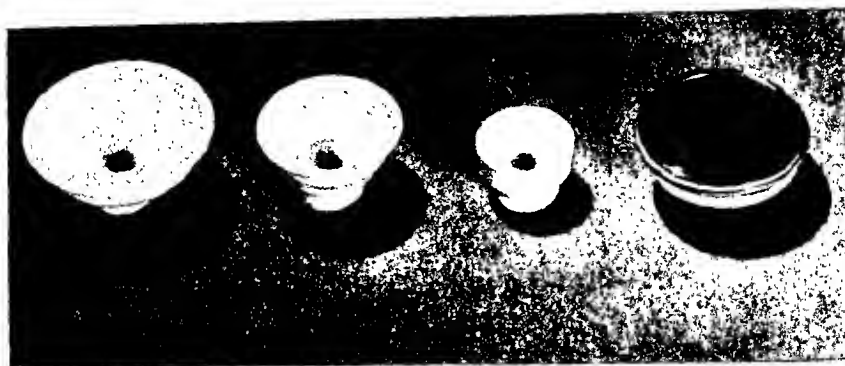


Fig. 3.—Chest pieces employed in verification of stethoscope bell theory.

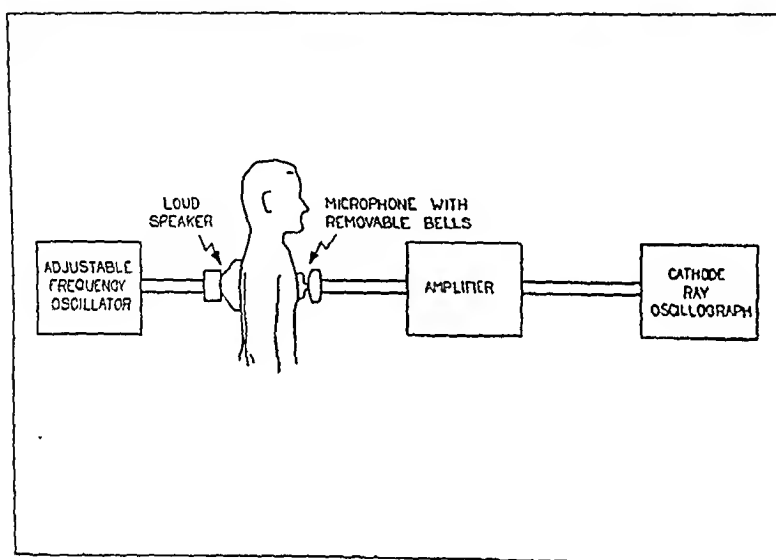


Fig. 4.—Schematic diagram of apparatus employed in obtaining Fig. 5.

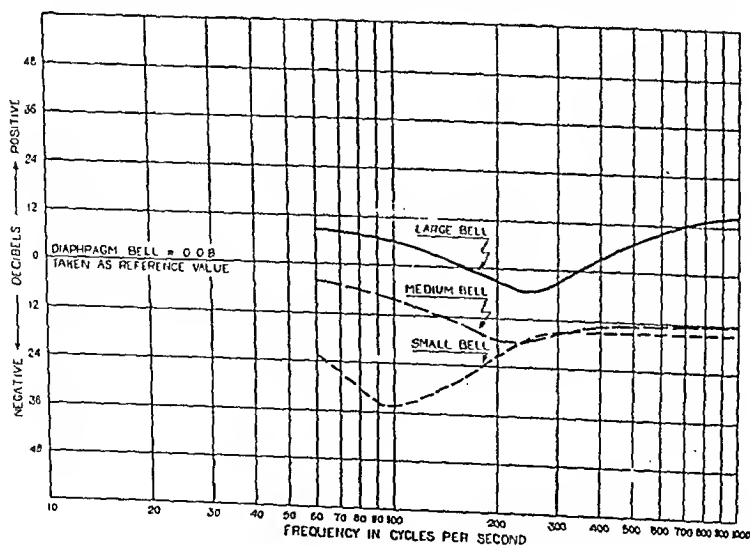


Fig. 5.—Resultant curves of the three open chest pieces, as compared with the efficiency of the chest piece. The higher the decibel reading, the higher the relative

front of the patient's chest. In other words, the adjustable frequency sound energy was fed into the patient's chest and picked up by the microphone and its associated bells; it was then amplified and fed into a cathode-ray oscillograph, used as a recorder. Normal pressure on the patient's chest was used with all four bells.

A frequency response curve was recorded for each bell. The curves thus obtained had practically no meaning, for they included the characteristics of the loud-speaker and the transmissional media of the chest. However, subtraction of one response curve from the other canceled the loud speaker and chest transmissional characteristics, thus allowing direct comparison of the respective bells. For our purpose, a comparison of the diaphragm bell with the open bells (using the diaphragm bell as a reference value) supplied useful information. In Fig. 5 the resultant curves of the three open bells and the diaphragm bell are compared; the reference value was zero decibels.

The dimensions of the four bells were as follows: The lip diameter of the large bell was 2.0 inches, of the medium bell, 1.5 inches, and of the small bell, 1.0 inch. The diaphragm bell was a typical "Bowles" chest piece, with a diaphragm 0.015 inch thick and a freely working diameter of  $1\frac{3}{8}$  inches. The internal volume of the large bell was 12.7 c.c., of the medium bell, 6.2 c.c., of the small bell, 2.3 c.c., and of the diaphragm bell, 2.5 c.c.

The following are some of the more important general conclusions that may safely be drawn from the graph of Fig. 5:

A. The efficiency of the three open bells improves, with respect to that of the diaphragm bell, as the frequency is decreased.

B. The larger the diameter of the open bell, the more efficient is the bell at the lower frequencies.

C. The large bell exhibits a resonance effect in the upper auscultatory region that is characteristic of a Helmholtz resonator of such dimensions. The resonance points of the smaller bells are above the auscultatory range and therefore are not shown in the graph.

It has been previously mentioned that a diaphragm bell is useful in bringing out certain high-pitched murmurs because it suppresses the lower frequency heart sound components that tend to mask the low intensity murmur of high pitch. The commonly used diaphragm bell, such as the Bowles of Fig. 3, employs a bakelite diaphragm 0.015 inch thick, with a freely working diameter of  $1\frac{3}{8}$  inches. This diaphragm was selected because clinical trial showed that it suppresses the lower pitches sufficiently well to bring out the higher pitched murmurs that are normally masked. Thicker diaphragms, or diaphragms with a higher natural period are not normally used because they produce such a pronounced over-all attenuation of the heart sounds that they are more of a disadvantage than an advantage. If the efficiency of the acoustic stethoscope could be increased enough to overcome the general reduction of sound intensity which occurs when thicker diaphragms are employed, the hard-to-hear, high-pitched diastolic murmurs might be more easily detected. This proved to be true when an amplifying stethoscope was employed; a diaphragm chest piece with a higher natural

period and an adjustable volume control was used. This test will be discussed in greater detail later. .

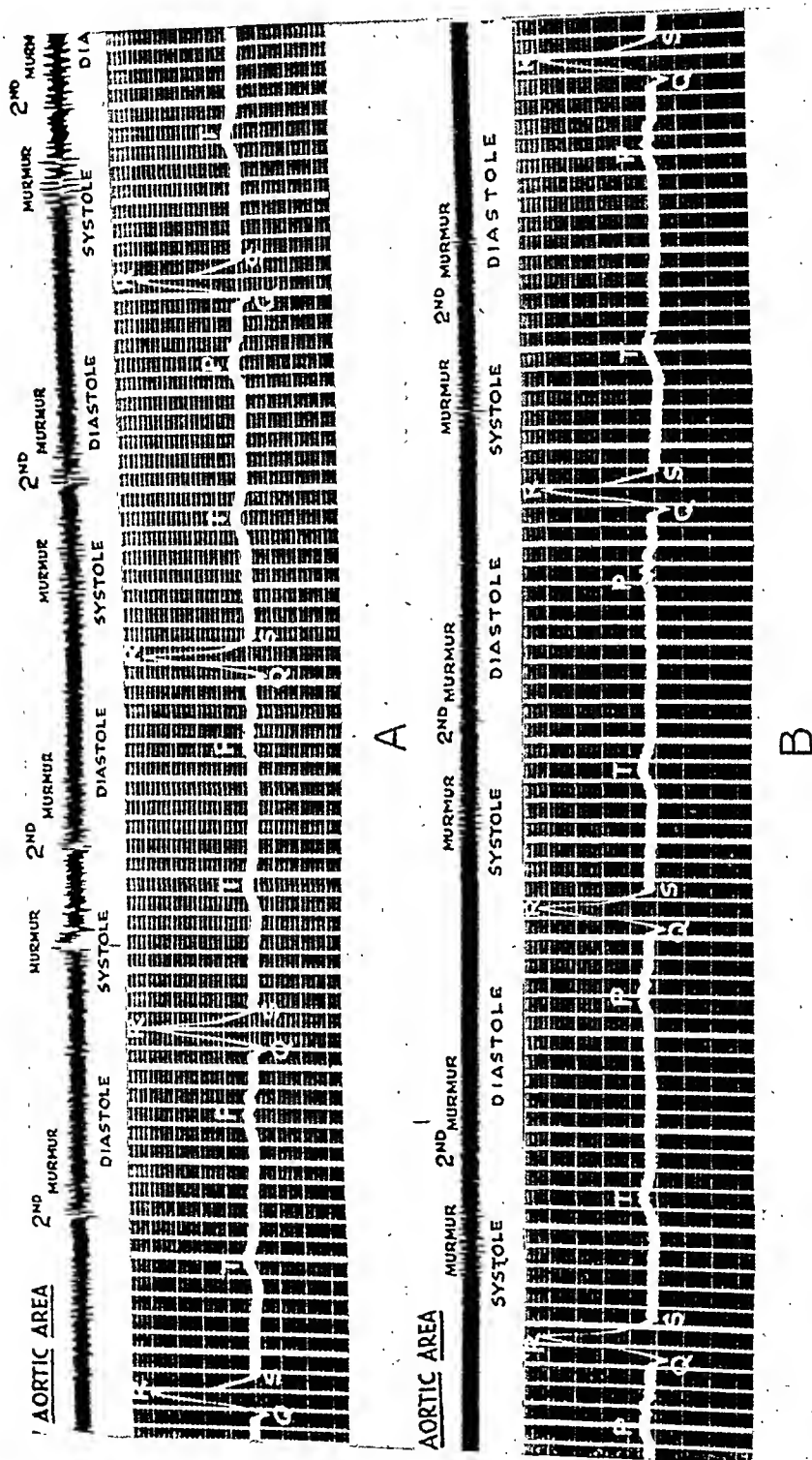


Fig. 6.—Graphic records of an aortic systolic and diastolic murmur. A, Taken with the large open chest piece of Fig. 3; B, taken with the diaphragm (Bowles type) chest piece of Fig. 3.

Fig. 6 shows two records which were obtained on a patient with an aortic systolic and diastolic murmur. Fig. 6A was made with the large

open bell of Fig. 3, and Fig. 6B with the diaphragm bell of Fig. 3 (bakelite diaphragm, 0.015 inch thick). The filtering action, or attenuation, of the low frequency components of the murmurs, as well as of the second heart sound (the only one present), is quite obvious. Systole and diastole may be timed accurately on the stethogram by recording the electrocardiogram simultaneously. The nature of the mechanism producing the records will also be discussed later.

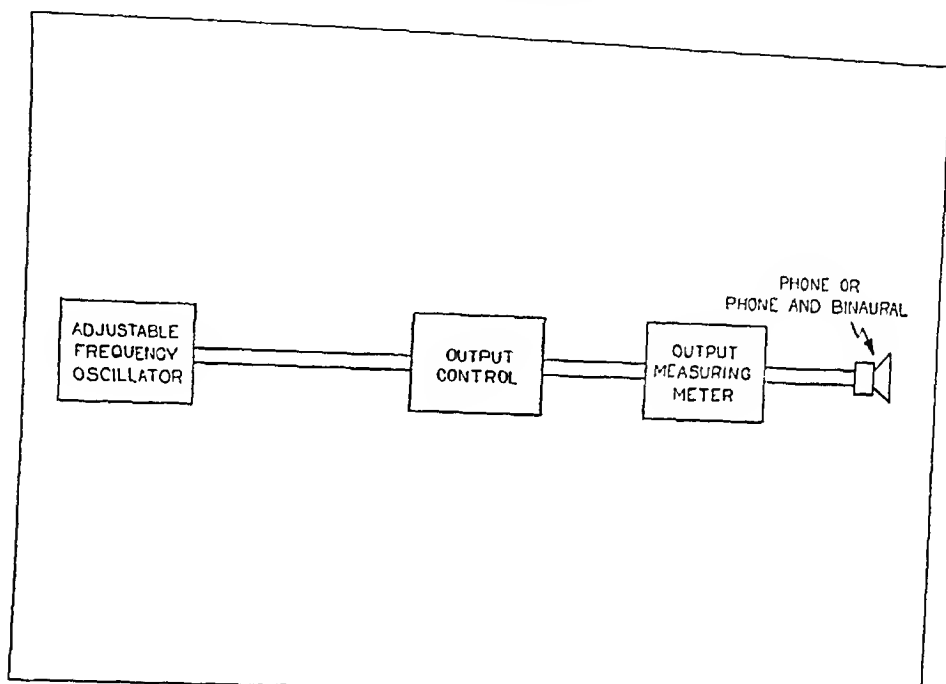


Fig. 7.—Schematic diagram of apparatus employed in determining the binaural effect.

*Binaural Effects.*—An experiment was performed in order to ascertain the effect of a binaural system in a stethoscope. Fig. 7 is a schematic diagram of the apparatus employed. An extremely quiet room was selected for the test (noise would definitely affect the accuracy of the test because it would alter the threshold of hearing).

The apparatus consisted of an adjustable frequency oscillator which was capable of producing a sinusoidal electrical wave practically free of any harmonic content. The frequency was adjustable over the auscultatory range. The electrical energy output at the various frequency settings was adjustable by means of a continuously variable control. The measured sinusoidal electrical waves were fed into a phone which could be placed to the ear of the person under test, or led to the ears through a binaural attachment.

The phone was applied to the patient's ear with a constant pressure throughout the test. For each frequency setting throughout the auscultatory range, the person who was being tested adjusted the output control to the point where the note was just audible, and the energy entering the phone was then measured. The same procedure was followed for the same phone with a binaural attachment.

If the resultant curves were plotted in decibels against frequency in cycles per second, we would have to take into consideration the characteristics of the phone, but, if the phone curve is subtracted from the binaural curve, the characteristics of the phone are canceled, and we obtain a direct ratio of hearing by the two systems. The reference level was taken as zero decibels, so that, if

any portion of the curve showed a positive decibel reading, it was an indication that the binaural system was more efficient by whatever the decibel reading happened to be; when the curve was negative, the monaural system was more efficient. Fig. 8 shows the resultant graph.

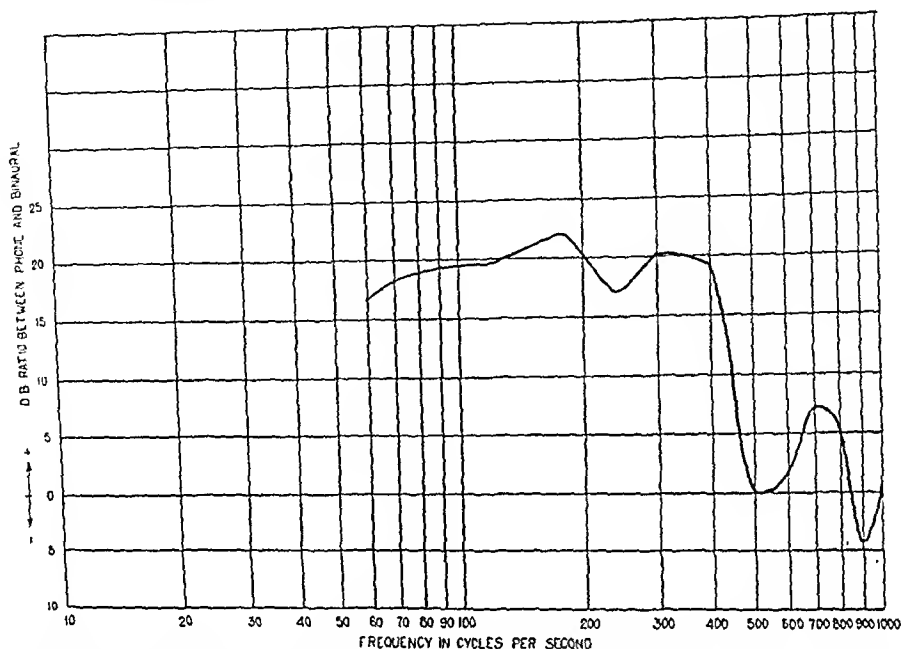


Fig. 8.—Relationship between monaural and binaural hearing in auscultation. Monaural hearing may be considered the equivalent of direct auscultation, whereas binaural hearing takes in the additive effect of both ears, minus the loss in efficiency of the stethoscopic attachment.

The following are some of the important relationships that exist between the monaural and binaral hearing systems in auscultation:

A. Direct telephone receiver application may be considered similar to direct auscultation.

B. A binaral system introduces resonance peaks, as may be seen in the graph.

C. In the range from 60 to 400 cycles per second, which includes most of the auditory range, the binaral system is, on an average, 20 decibels better than the monaural; this is equivalent to a tenfold increase in sound pressure at the eardrum at the threshold level.

D. Only between 850 and 1,000 cycles per second is monaural or direct auscultation more efficient than binaral, and this range is too high to be useful in auscultation.

*Effects of Tubing Dimensions.*—An important consideration pertaining to stethoscope performance is the length and caliber of the rubber tubing. It was previously mentioned that the pressure variations at the ear, produced by the motion of the skin or bakelite diaphragm, are inversely proportional to the internal volume of the stethoscope, so that an infinitely small volume would theoretically exhibit a maximum variation in pressure, which, in turn, would manifest itself as a sound of maximum intensity. Obviously, therefore, the tubing should be as short as possible, and the caliber as small as possible. The wall of the tubing should be sufficiently



rigid for maximum efficiency, for any wall motion reduces the effective pressure variation transmitted to the observer's ear.

A factor that must be taken into consideration is the frictional resistance offered to the air column by the walls of the rubber tubing. In other words, the efficiency of a stethoscope decreases as the resistance to the pressure variations is increased; the resistance is increased as the caliber is decreased. In order to eliminate the resistance component we have still to consider that the greater the volume, the less the efficiency. Therefore, to obtain the most efficient tubing for a stethoscope, one should make the tubing as short as possible and compromise on the resistance and volume components. The compromise may be approached by plotting a graph representing efficiency versus volume effect, and another representing efficiency versus resistance effect; where the two curves intersect is the point of optimum efficiency.

A test was performed to ascertain the actual change in efficiency of a binaural system caused by lengthening the rubber tubing. The apparatus employed in the experiment was identical with that shown in Fig. 7. The conditions under which the testing was done were the same as when the "Binaural Effect" experiment was performed. The only difference in the entire test was that a threshold of hearing curve (plotted in decibels input to the telephone receiver to produce the threshold of hearing level against frequency in cycles per second) was obtained for the phone and binaural attachment for various lengths of tubing. Two tubes were used to connect the binaural to the phone (audiphone, which will be described later). Fig. 9 shows the curves obtained with the three sets of tubing, which were 26 inches, 12 inches, and 3 inches long, respectively.

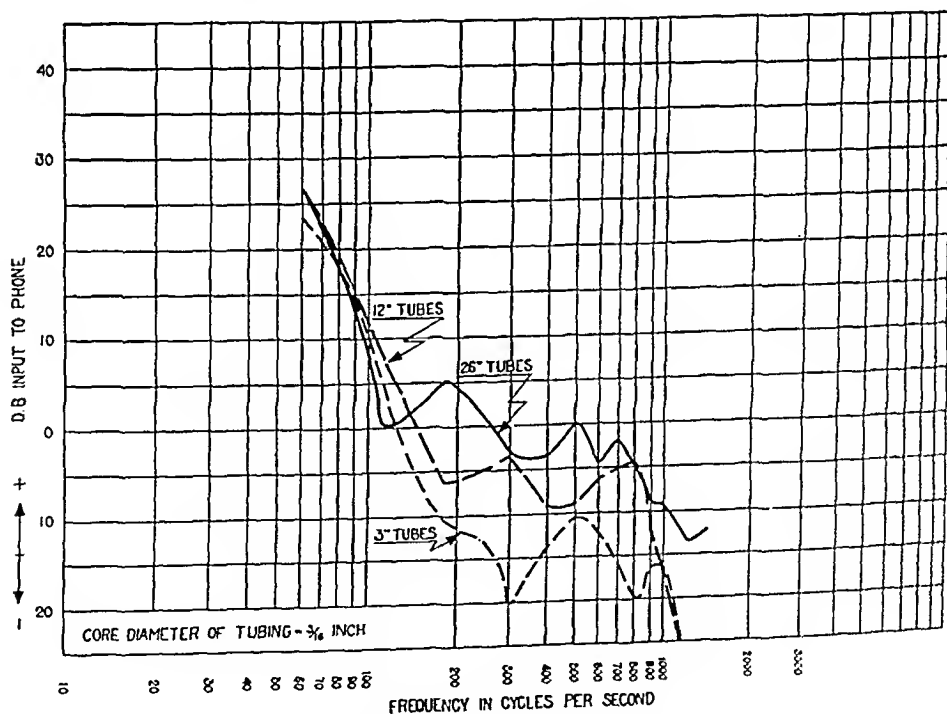


Fig. 9.—Curves illustrating transmissional losses in a binaural stethoscope as a result of increased tubing length.

The following are the general conclusions that may be drawn from a comparison of the three curves:

A. Below about 100 cycles per second, the efficiency is not affected materially by tubing length.

B. From about 100 cycles per second to 1,000 cycles per second, tubing length exhibits a considerable effect upon the efficiency; that is, the efficiency decreases with increased tubing length.

The changes in the efficiency of an acoustic stethoscope which are caused by varying the length of the tubing, although they are not given any consideration by stethoscope users, produce an effect upon the quality of the heart sounds. For example, at 200 cycles per second there is a 15-decihel attenuation of the sounds when two rubber tubes, each 26 inches long (commercial stethoscope tubing, with a caliber of  $\frac{3}{16}$  inch) are substituted for two similar tubes 3 inches in length. The sound would be eight times as loud in the short tubing system. This attenuation occurs in the region where the low intensity, high-pitched diastolic murmurs are present, and every possible increase in efficiency in this region is of utmost value.

## VI. COMBINED AMPLIFYING STETHOSCOPE, STETHOGRAPH, ELECTROCARDIOGRAPH, AND SPHYGMOGRAPH

*Introduction.*—From the material presented thus far, in which the factors involved in auscultation are considered from a physiologic and physical point of view, we may safely conclude that the human ear, when operating in conjunction with an acoustic stethoscope, has many faults. In this paper several modifications in the design of the acoustic stethoscope have been suggested, with the purpose of increasing the auditory sensation efficiency of some of the sounds which are difficult to register. No doubt exists that, in the future, additional minor improvements may be developed in the acoustic stethoscope. However, after a thorough study of the physical behavior of the acoustic stethoscope, it appears that there is little room for radical improvements because of the inflexible properties common to the instrument as well as to human hearing.

Such a prediction concerning the future of the acoustic stethoscope appears rather bold, but, if average hearing is an unalterable constant, there remains only the acoustic stethoscope as the adjustable compensator for the defects of normal hearing. The physical make-up of an acoustic stethoscope is not very flexible; this is true of most pure acoustic systems. Until recently, a somewhat similar situation existed in the science of acoustics. Very little progress could be made in the study of acoustics, as well as the psychology and physiology of hearing, beyond a certain point, because of the inflexibility of the purely acoustic or acoustic-mechanical instruments which were available. This situation is well described in the recently published text "Hearing—Its Psychology and Physiology,"<sup>23</sup> by Dr. Stanley Stevens and Dr. Hallowell Davis, of Harvard University. With the adaptation of electronics to acoustics and the allied studies in the psychology and physiology of hearing, a new approach to the subject has been opened.

In a similar manner, the application of electronic, electromagnetic, and piezoelectric devices to auscultation has made possible a practically unlimited degree of freedom in the control of the over-all performance of pick-up device and ear, whereas, in the case of the purely acoustic stethoscope, flexibility in the control of this performance is limited. That is, there is sufficient freedom of adjustment in these more modern devices to allow certain modifications to be made in order to compensate for some of the auscultatory failings of the human ear.

In spite of the fact that such unlimited compensatory adjustments may be made, with certain decided improvements in the form of increased audibility of some physiologic chest and heart sounds, some of the inherent shortcomings of hearing cannot be overcome. This problem is summed up by Wiggers,<sup>24b</sup> as follows:

“Most of the vibrations of the chest wall inaugurated by the two sounds of the heart have an amplitude and frequency which approach the lower auditory limit; indeed, it is probable that some of the vibrations are incapable of being recognized by the ear. While the auditory appreciation for slow vibrations of low frequency lasting only for brief moments can be cultivated by practice and training, the average ear and brain have some difficulty in differentiating the finer differences in time, frequency, and form, shown to exist in graphic records. When waves of several frequencies intermingle, the ear, according to inclination or training, tends to pick out one group and to suppress the other.”

In addition to what we may consider the normal faults of the human ear as regards auscultation, another important condition must be taken into consideration. Many physicians who are under the impression that their hearing is normal will be found to have an audiogram which shows peaks and valleys in the auscultatory frequency region. The audiogram valleys in many cases fall well below the threshold of hearing for some of the important sounds. This characteristic of hearing has a tendency to become more exaggerated as the physician ages. The result of such changes is that certain sounds become inaudible to the doctor without his being aware of the fact.

Such shortcomings of hearing, whether normal or subnormal, may be surmounted by supplementing auscultation with graphic recording. A graphic recording system designed especially to record the required frequency band is immune to the auditory defects of the ear.

*History.*—At the turn of the century, attempts were made to improve auscultation by means of acoustic and electroacoustic devices. The experiments as a whole ended in failure when purely acoustic means were employed. An electroacoustic system was devised which did succeed in amplifying the sounds, but excessive distortion made the instrument useless. The electroacoustic stethoscope operated on a principle similar to that of the telephone; it consisted of a carbon-granule microphone which modulated an electric current, and this, in turn, excited a telephone receiver.

Successful amplification of the sounds was made possible by the development of the audion tube. Although the history of electronic amplification dates back to the practical results obtained by de Forest<sup>25</sup> in 1907, the audion tube amplifier was not sufficiently reliable for practical auscultatory application until a few years ago.

One of the earliest, practical, amplifying stethoscopes was developed by the Western Electric Company<sup>26, 27</sup> in 1924. Several other experimenters produced electronic-type amplifying stethoscopes. Since these devices altered the quality and character of the sounds so much that auscultatory technique had to be relearned, their clinical usefulness was decidedly limited.

Investigators such as Battaerd,<sup>28</sup> Brömser and Frank,<sup>29</sup> Crehore and Meara,<sup>30</sup> Einthoven,<sup>31</sup> Geluk and Einthoven,<sup>32</sup> Fahr,<sup>33</sup> Frank,<sup>34-36</sup> Gerhartz,<sup>39</sup> Hermann,<sup>40</sup> Lilienstein,<sup>41</sup> Myres,<sup>42</sup> Ohm,<sup>43</sup> Wiggers and Dean,<sup>44</sup> Williams,<sup>45</sup> Sell,<sup>92, 93</sup> Trendelenburg,<sup>94-96</sup> and others, realizing the clinical limitations of human hearing, made the earlier attempts at recording the heart sounds.

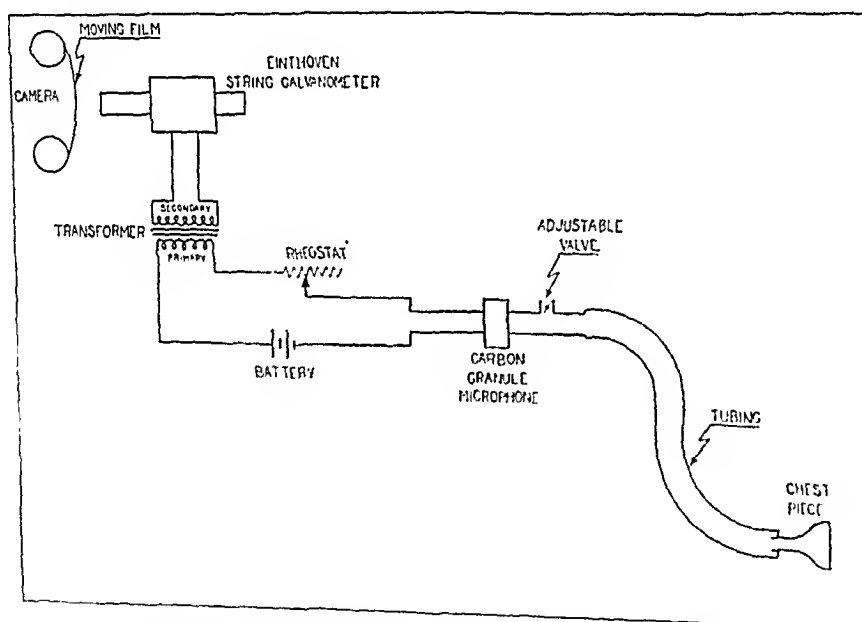


Fig. 10.—Schematic sketch of Einthoven's phonocardiograph.

One of the earliest types of recording stethoscopes that had some practical value was the Einthoven phonocardiograph. Fig. 10 shows a schematic sketch of the apparatus. A typical stethoscope chest piece was employed for accumulating the sounds, which were directed to a carbon-granule microphone. Interposed between the chest piece and the microphone was an adjustable leak valve, which was used to regulate the amount of low-frequency heart sound component reaching the microphone. The microphone performed the function of converting the minute sound pressure variations in the tubing into electrical pulsations whose intensity was adjustable by means of the rheostat; these electrical pulsations were allowed to pass through the primary winding of the transformer. The transformed electrical

pulsations were led off the secondary winding of the transformer and passed through the metallic-coated quartz string of the galvanometer. The purpose of the transformer was to prevent the direct current polarizing potential, produced by the battery which operated the microphone, from passing through the galvanometer string. The tension of the galvanometer string was greater than that employed in making electrocardiograms; this allowed the string to record the higher pitched sounds. The oscillations of the string were photographed in the usual electrocardiographic manner, thereby producing a phonocardiogram, as Einthoven preferred to call the graphic sound record. Einthoven could listen to the sounds by placing a telephone receiver across the secondary winding of the transformer.

Although the Einthoven phonocardiograph was capable of recording the heart sounds graphically, it was far from being a satisfactory apparatus for the following reasons:

A. Einthoven could not produce a smooth base line when no physiologic sounds were present, because extraneous noises entered the system through the leak valve. The undamped carbon particles of the microphone also produced extraneous noises.

B. The transformer employed by Einthoven introduced considerable distortion; understanding of audio-transformer performance was very limited at that time.

C. The sounds heard by placing a telephone receiver across the secondary winding of the transformer were so distorted as to be hardly recognizable.

Einthoven, although decidedly handicapped by the lack of suitable apparatus, did succeed in obtaining much valuable information concerning the nature of heart sounds.

The earlier investigators met with some success in registering heart sounds by the direct method, which is a system employing the physical principles of the human ear. The apparatus is usually composed of a stethoscope bell connected to a sensitive membrane by means of a rubber tube. The movements of the membrane produced by the cardiac sounds are recorded by means of an optical system focused upon a moving photographic film. The membrane in the direct system of heart sound recording may be compared with the tympanic membrane of the ear and is usually constructed of either thin rubber, mesentery from the guinea pig, gelatin, soap film, isinglass, or other such materials.

One of the most successful early stethographs was devised by H. B. Williams. It consisted of an electromagnetic telephone receiver operating in reverse as a microphone. The minute electrical pulsations were then intensified by means of a four-stage audion amplifier and recorded with an Einthoven string galvanometer. The Western Electric Stethophone<sup>19</sup> operated on essentially the same principle as the Williams apparatus. Trendelenburg's stethograph employed a condenser type of microphone, and Sell's apparatus employed an electrodynamic type of microphone, operating with a multistage amplifier and a moving-coil galvanometer. In recent years the piezoelectric crystal has been used as an element of the heart sound microphone.

The improvements incorporated by Williams, Sell, Trendelenburg, the Western Electric Company engineers, and others, although notable, did not succeed in reproducing the heart sounds with the fidelity with which they could be heard with the ordinary acoustic stethoscope or by immediate auscultation. The relationship between hearing and recording was extremely vague.

We shall now describe an apparatus that reproduces sounds without the slightest noticeable alteration in quality, and a method of recording the sounds simultaneously with the electrocardiogram and sphygmogram.

*General Considerations.*—An amplifying stethoscope, as the name indicates, is an apparatus which is capable of increasing the intensity of sounds; this may be accomplished either electrically, piezoelectrically, electronically, acoustically, mechanically, or electromagnetically, or by any combination of these methods. The following are some of the more important factors that must be taken into consideration in designing an amplifying stethoscope:

1. The apparatus must be capable of reproducing sounds without altering their character.

2. The amplifying stethoscope must be free of any inherent noise and be immune to the influence of external electrical wiring, diathermy machines, x-ray apparatus, etc.

3. Normal room noises and vibrations should not affect the operation of the apparatus.

4. The intensity of the sounds should be controllable by means of an easily adjustable, calibrated volume control.

5. The apparatus must be free of feed-back howls and squeals when the chest piece or sound pickup unit is brought into the vicinity of the hearing device.

6. The apparatus must be capable of standing rough handling.

7. It is advantageous to make the apparatus independent of house current, for the proper current and voltage are not universally obtainable.

8. The frequency response characteristic of the amplifying stethoscope should be of such a nature as to overcome, whenever possible, the natural human hearing defects which interfere with auscultation.

The stethograph, or heart sound recording mechanism, must be capable of performing the following functions:

1. It must record graphically all of the sounds that are audible with the stethoscope.

2. It must be capable of recording sounds that are easily missed as a result of masking and other phenomena caused by natural defects of the human ear.

3. When there are no sounds, i.e., during normal systole and diastole, the base line must be reasonably smooth.

4. The stethograph mechanism must be immune to all types of external electrical interference.

The electrocardiograph must be capable of satisfying all of the accepted standards and requirements. The electrocardiogram should be recorded simultaneously with the stethogram, in order to time properly the events of the cardiac cycle. Some stethograms are meaningless or confusing without a simultaneously recorded electrocardiogram or sphygmogram; this point will be illustrated later.

*General Component Relationships.*—Fig. 11 is a schematic illustration of the interrelationship between the various components of an apparatus which is capable of producing, simultaneously, an electrocardiogram-stethogram and amplified heart sounds.

The amplifying stethoscope component consists of a microphone which serves to convert the sound energy picked up at the chest wall into equivalent, minute, electrical pulsations. These minute electrical pulsations are passed into an electron-tube amplifier, and the amount of amplification is regulated by a volume control device. The audiophones, which are connected to the output of the amplifier, reconvert the strengthened electrical pulsations into sound energy which is identical with that picked up by the microphone.

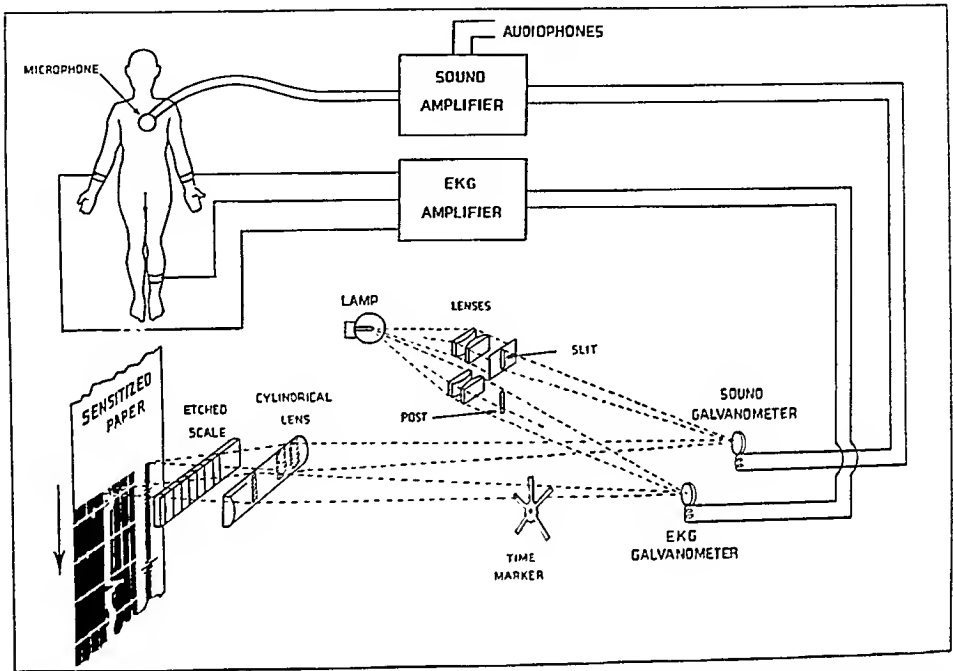


Fig. 11.—Schematic diagram illustrating the interrelationship of the various components of an apparatus capable of producing a simultaneous electrocardiogram-stethogram and amplified heart sounds.

A moving-coil (d'Arsonval) galvanometer which is capable of responding to the frequency band of the sounds encountered in auscultatory work is also connected to the output of the sound amplifier. The galvanometer coil, which carries a mirror, oscillates in response to the intensified electrical pulsations. A beam of light is reflected from the mirror upon moving, sensitized film or bromide paper. The oscillation of the mirror moves the light beam across the paper. The combination of the longitudinal motion of the paper and the transverse movement of the light beam produces a graph of the sounds, plotted against time (a stethogram).

The electrocardiogram is obtained by directing the cardiac currents into a proper switching and standardizing system, amplifying or strengthening the minute currents, and feeding them to another moving-coil (d'Arsonval) galvanometer whose frequency characteristics are suited to electrocardiography. By means of a suitable optical system, the movements of the galvanometer coil are recorded on the same sensitized paper or film upon which the heart sound beam falls, thereby producing a simultaneous electrocardiogram-stethogram. Vertical time marking lines, together with horizontal amplitude lines, are superimposed optically over the electrocardiogram section, which occupies 4 cm. of a 6-centimeter-wide film or paper; the remaining 2-centimeter band is devoted to the stethogram.

*The Microphone.*—The invention of the telephone and the successful transmission of a complete sentence by Alexander Graham Bell in 1876 marked the beginning of the development of devices capable of converting sound energy into electrical energy. The development of the fundamental principles of nearly all microphones (technically known as electroacoustic transducers) which are in use today dates back to Bell's time, but, until recently, the microphones could not be used because they were not sensitive enough. The perfection of the vacuum-tube amplifier in recent years has made it possible to take advantage of many of the desirable properties of these electroacoustic transducers.

A microphone is an electroacoustic transducer which, when actuated by the power in an acoustic system, will deliver power to an electrical system, and the wave form in the electrical system will correspond to that in the acoustic system.

When Einthoven performed his experiments with the phonocardiograph, he did not have an electronic type of amplifier. As a result, he was forced to employ a microphone which was not dependent upon electronic amplification. The best transducer available was the carbon-granule microphone.<sup>48, 49</sup> As previously observed, this type of transducer, when employed for stethographic purposes, possessed many limitations. H. B. Williams improved upon the Einthoven system by substituting a magnetic type of telephone receiver to whose diaphragm a nonmetallic button was cemented. The button was placed in contact with the patient's chest, so that the sound vibrations were transmitted mechanically to the diaphragm. The vibrating diaphragm, in turn, induced an equivalent electromotive force in the coil of the electromagnet of the telephone receiver. The coil was electrically connected to a step-up transformer which fed into an amplifier.

Although Williams' microphone was a decided improvement over the one employed by Einthoven, in that it eliminated the background noise caused by the carbon granules, it possessed some undesirable qualities, as follows:

1. The Williams microphone required a coupling transformer between the microphone and amplifier. If a transformer is followed by a highly sensitive amplifier, minute alternating current interferences may be picked up from electrical appliances by the transformer, amplified, and superimposed upon the heart sounds.

2. When the ear piece (the device which reconverts the amplified electrical pulsations into amplified sounds) was not kept well away from the microphone, an electromagnetic feed-back took place and a howling sound was heard.

3. Considerable difficulty was encountered in subduing extraneous noises caused by slight shifting of the microphone contact button on the patient's chest, unless the microphone was carefully fastened down with adhesive tape. This is a rather awkward clinical procedure.

Sell, in an endeavor to improve upon the Williams apparatus, constructed an electromagnetic microphone. It consisted of a magnet and a movable coil. The coil was physically connected to a button which was in contact with the patient's chest. A double-walled, suction type of funnel surrounded the microphone button. The microphone was operated by suspending the unit from a cushioned pulley, and fastening the suction bell to the patient's chest. This arrangement placed the microphone button in contact with the chest and thereby provided for transmission of the sound vibrations to the coil. The vibrating coil, in turn, cut the lines of force produced by the fixed magnet, setting up an electromotive force in the coil. The coil was electrically connected to a transformer, followed by an amplifier, as in the case of the Williams apparatus.

The major improvement in the Sell microphone was in the construction of the chest piece, which eliminated to a large extent the extraneous noises caused by slight shifting of the button on the chest. The other undesirable features of the Williams microphone were also present in the Sell microphone, for the general nature of the two was the same.



The suction bell functioned very well when there was no heavy growth of hair on the chest. However, in cases in which hair was present, the suction could not be maintained, and the chest had to be shaved. The application of an oily substance, such as vaseline, on the patient's chest often helped maintain the vacuum if the hair was not dense.

Trendelenburg devised a microphone which operated on the electrostatic principle. It is better known as a condenser type of microphone. In its simplest form, a condenser microphone comprises a light, stretched, metallic diaphragm, spaced at a very short distance from another, parallel, metallic plate, which acts as a fixed electrode. A steady, direct-current, polarizing potential, such as that used with the carbon-granule microphone, but of considerably higher value (usually about 135 volts), is placed across the parallel plates through a series resistance. The minute, alternating variations of capacity caused by the movements of the diaphragm under heart sound excitation create a variable impedance which produces an alternating current that is equivalent in character to the heart sounds. The generated alternating current flowing through the resistor, which is connected in series with the microphone, sets up an equivalent alternating potential across the resistor, and this is fed to an amplifier and intensified.

The Trendelenburg microphone employed a suction bell similar to that of the Sell microphone, with the exception that the chest wall motions were transmitted to the diaphragm through an air column instead of by direct mechanical contact. Trendelenburg's microphone was far superior to the previously mentioned types, in that it eliminated the electromagnetic feed-back howl when an electromagnetic ear piece was employed. However, two major faults still remained, namely:

1. The characteristically low sensitivity of a condenser type of microphone necessitates the use of an amplifier possessing considerably more amplification and a higher degree of instability.

2. When relatively high pressures are suddenly set up in the air column of a condenser microphone, for example, when the bell is applied to the patient's chest, the diaphragm tends to be forced over to the other plate electrode. Because there is a polarizing potential between the two electrodes of the microphone, pitting of the metal takes place at the point of contact every time the electrodes touch. After a number of such contacts, the microphone becomes inoperative.

The electrical impedance of a microphone may vary anywhere between a few ohms and many hundreds of thousands of ohms, depending upon the type. For satisfactory operation, the electrical impedance of a microphone must match the impedance of the following circuit element. In the case of an electromagnetic type of microphone, such as that of Sell or Williams, the impedance of the coil must be properly matched. The impedance of such a coil (depending upon the design) may vary between a few ohms and several thousand. Therefore, in order to match such an element to an amplifier and retain maximum efficiency and a minimum of distortion, a coupling transformer must be introduced in such a way that the primary winding of the transformer matches the microphone coil, and the secondary winding of the transformer matches the amplifier.

In the case of a condenser microphone, such as the Trendelenburg type, the inherent impedance is extremely high, and of the same order as the input of an amplifier. As a result, no coupling transformer is necessary. Thus, some of the previously mentioned difficulties which are encountered when a transformer is placed in so delicate a location may be eliminated.

During the last few years the radio manufacturers have perfected the piezoelectric crystal microphone. A crystal microphone is one in which the electrical output is dependent upon the stresses set up in a crystal

of rochelle salt, quartz, or tourmaline. In such a device the output potentials are proportional to the stresses which the sound waves induce. Rochelle salt crystals are most commonly used in crystal microphones because the piezoelectric constant of rochelle salt is more than one thousand times that of quartz and tourmaline.

The piezoelectric crystal element possesses many characteristics which make it suitable for stethography; the following are some of the most important:

1. The crystal element is inherently free of noises.
2. The crystal element is small and light and requires only electrostatic shielding.
3. It does not require any polarizing potentials.
4. The impedance of a crystal element is of such an order that a coupling transformer is not required.
5. The output level (voltage output vs. excitation) is quite high as compared with other types of microphone elements.
6. The crystal element is comparatively rugged.

When all of the advantageous properties of the crystal microphone are considered, it will be understood why such an element was chosen for our microphone.

A detailed technical discussion of the design and mathematical theory of crystal microphones which are suitable for stethographic, as well as auscultatory, work is obviously beyond the scope of this paper. However, a general consideration of some of the more important features should be of interest.

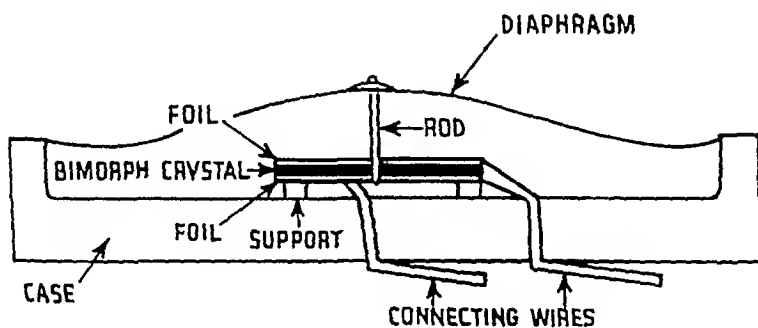


Fig. 12.—Cross-section sketch of the crystal microphone cartridge.

The heart of the microphone is a cartridge or diaphragm type of crystal unit (Fig. 12). It consists of a curvilinear diaphragm which is directly coupled to a bimorph rochelle salt crystal through a tiny connecting rod; the crystal and connecting rod are located in the interior of the cartridge. Should an actuating force be applied to the diaphragm, proportional stresses will be set up in the crystal, and it will transform these stresses into equivalent electrical potentials which are conducted away from the crystal by means of metallic foil electrodes in contact with it.

The fundamental frequency, or natural period, of the bimorph crystal is approximately 10,000 cycles per second. When a diaphragm is coupled to the crystal

(Fig. 12), the fundamental frequency of the combination is lowered to a few thousand cycles per second. This is still well above the upper frequency limits encountered in auscultatory work.



Fig. 13A.—Microphone case, with built-in, acoustic, high-pass filter, and piezoelectric cartridge.

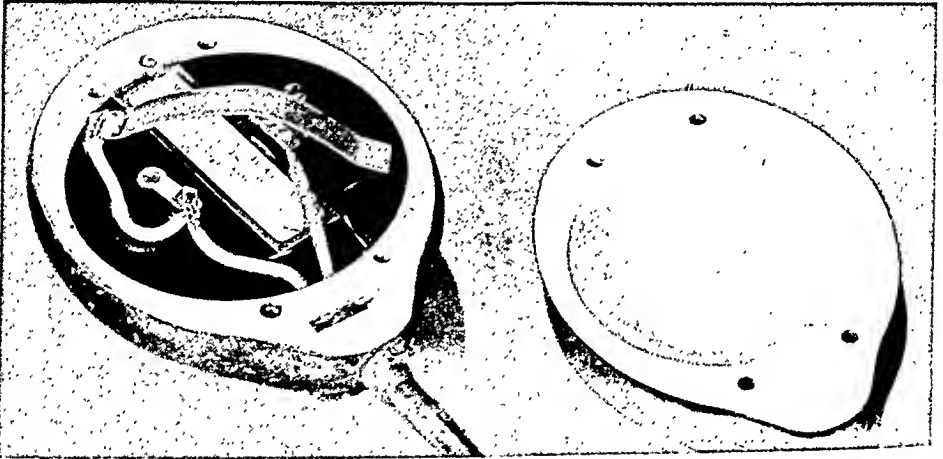


Fig. 13B.—Manner in which cartridge is inserted into microphone case.

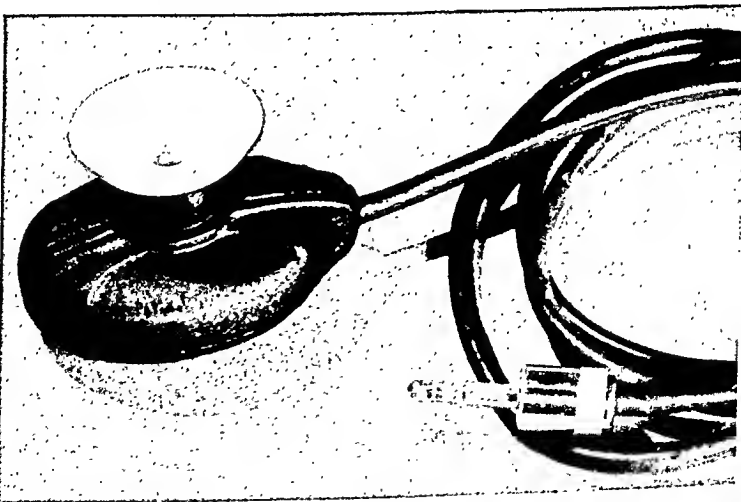


Fig. 13C.—Completely assembled microphone, with a large, open chest piece.

The cartridge is fitted into a case especially designed for stethography (Fig. 13A, B, C). The microphone case proper is constructed to incorporate what is technically known as an acoustic high-pass filter. The filter serves two essential purposes,

namely: (1) It eliminates the extremely low-frequency, chest wall motions which have no known physiologic significance. (2) It protects the crystal from sudden, high pressures of extremely low frequencies, such as those which are produced by applying the microphone to the chest.

A filter, whether it be electrical, mechanical, or acoustic, is a system which will freely pass desired frequency bands, and highly attenuate neighboring, undesired bands. Campbell<sup>57</sup> is credited with having developed the electrical type of filter; Stewart<sup>58</sup> devised the first acoustic types. The mechanical type of filter has been employed in various kinds of apparatus for many centuries. The electrical wave-filter action has been further investigated by Zobel,<sup>59</sup> Johnson,<sup>60</sup> Shea,<sup>61</sup> and others; the acoustic filter, by Mason<sup>62</sup>; and the mechanical types, by Crandall.<sup>63</sup> The most complete investigations on filtering action have been carried out for electrical types. However, the analyses of the acoustic and mechanical types of filters are applicable and are very similar to those of the electrical types.

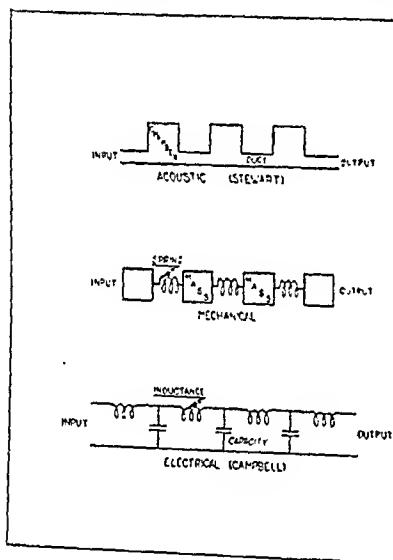


Fig. 14.—Equivalent low-pass filters.

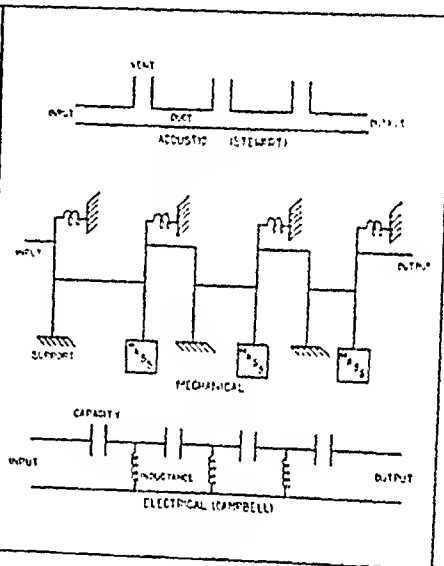


Fig. 15.—Equivalent high-pass filters.

Fig. 14 shows three equivalent filters which possess low-pass characteristics. These filters are known as two-element types because each element contains two components. The condenser in the electrical circuit, the chamber in the acoustic filter, and the spring in the mechanical filter perform corresponding functions. The inductance in the electrical filter performs a function similar to that of the duct in the acoustic filter and the mass in the mechanical filter. Fig. 15 shows three equivalent filters which have high-pass characteristics. Theoretically, a low-pass filter should allow the passage of electrical currents, velocities, and volume currents, in electrical, mechanical, and acoustic systems, of all frequencies lying between zero and the filter cutoff frequency, which is dependent upon the constants of the filter. On the other hand, a high-pass filter will allow the passage of currents, velocities, and volume currents, in electrical, mechanical, and acoustic systems, of all frequencies between the cutoff frequency and everything above it to infinity.

The carbon-granule microphone employed by Einthoven in his phonocardiograph possessed a simple, but crude, sort of high-pass acoustic filter. Einthoven accomplished the filtering process by introducing an adjustable valve (Fig. 10). The fact that Einthoven allowed access between the external air and the air column which was under heart sound excitation was one of the main causes for the introduction of extraneous noises.

In our crystal microphone, the acoustic filter channels are so constructed that they connect with a chamber hermetically sealed into the microphone case; the chamber acts as a substitute for the external air. This type of acoustic filter design has made possible the necessary degree of high-pass filtering action upon the heart sounds, without introducing the slightest traceable extraneous noise.

The four bells, or chest pieces, of Fig. 3 are used in conjunction with the microphone. Each bell, as previously pointed out, produces a different degree of filtering action. The desired bell may be screwed into the microphone case.

*The Audiophone.*—In an amplifying stethoscope, the audiophone is the component which converts the amplified electrical pulsations into equivalent sounds such as those which are normally heard with the acoustic stethoscope. Fig. 16 is a photograph of an audiophone. The three fundamental components of an audiophone are the electroacoustic transducer, the case, and the binaural.

The electroacoustic transducer portion of the audiophone is an electromagnetic telephone receiver of the diaphragm armature type. A telephone receiver is an electroacoustic transducer which, when actuated by an electrical system (the amplifier, in the case of a stethograph), will supply power to an acoustic system, and the wave form of the sound in the acoustic system will correspond to the wave form in the electrical system. Telephone receivers may be divided into four general classes, namely, (1) electromagnetic, (2) electrodynamic, (3) electrostatic, and (4) piezoelectric. Complete descriptions of the electromechanics of these electroacoustic transducers may be found in most good texts or handbooks on applied acoustics,<sup>64</sup> telephony,<sup>48</sup> and electrical engineering.<sup>66</sup> The electromagnetic type, which was invented by Alexander Graham Bell and perfected by others, was selected as the audiophone component because of its simple construction, rugged nature, ability to cover the required frequency band, compactness, and suitable impedance characteristics.

The telephone receiver first developed by Bell consisted of an electromagnet which retained a residual amount of magnetism. The strength of the residual magnetic field could be modulated by the electric signal which was allowed to pass through a coil wrapped around the magnet. A steel diaphragm, clamped at its circumference and placed a short distance from the pole pieces of the electromagnet, was caused to vibrate at a frequency and to a degree which depended upon the frequency and strength of the signal current. The diaphragm action, in turn, set the surrounding air into motion, and this produced the sound which was perceived by the ear. The present-day instruments operate on the same principle, but improved materials and design have greatly increased their efficiency and sensitivity.

The only moving part in an electromagnetic receiver of the diaphragm armature type is the diaphragm. Although the system appears extremely simple from a mechanical standpoint, the theoretical analysis is very complex. Theoretical investigations of the apparatus have been made by Crandall,<sup>63</sup> Kennelly,<sup>66</sup> Lamb,<sup>67</sup> and several others. All seem to agree that the mechanics of the diaphragm resembles very closely that of an ideal, clamped, circular plate.

In the design of the electroacoustic transducer which is employed in the audiophone, a diaphragm with a fundamental resonance peak of roughly 1,000 cycles per second was selected. Following this resonance point, other resonances occur as the frequency is increased. The fundamental resonance and certainly the higher frequency modes of vibration are well above the auscultatory frequency band and, therefore, produce no ill effects.

The acoustic system in an audiophone consists of the inertance produced by the binaural system and the capacitance of the volume which is excited by the diaphragm. In an analysis of the action of an audiophone, the acoustic system, as well as the mechanics of the diaphragm, must be considered.

In an ideal audiophone, the ratio of sound pressure variation delivered to the ear cavity to the voltage applied to the transducer should be independent of the frequency. If we make the assumption that the cavity of the ear presents a constant

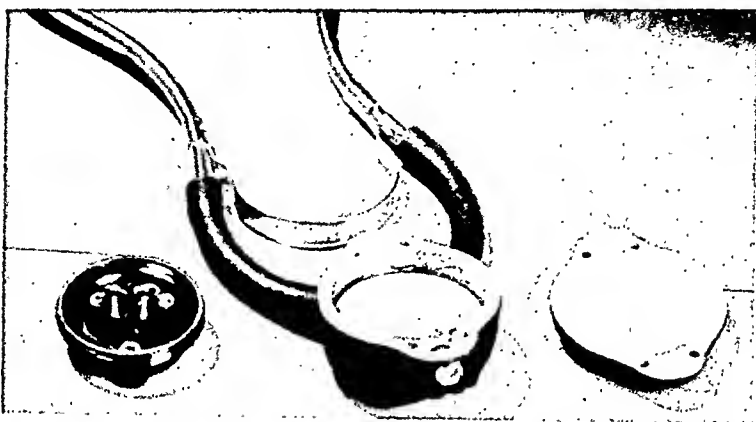


Fig. 16A.—Audiophone, with cover and electromagnetic phone removed.

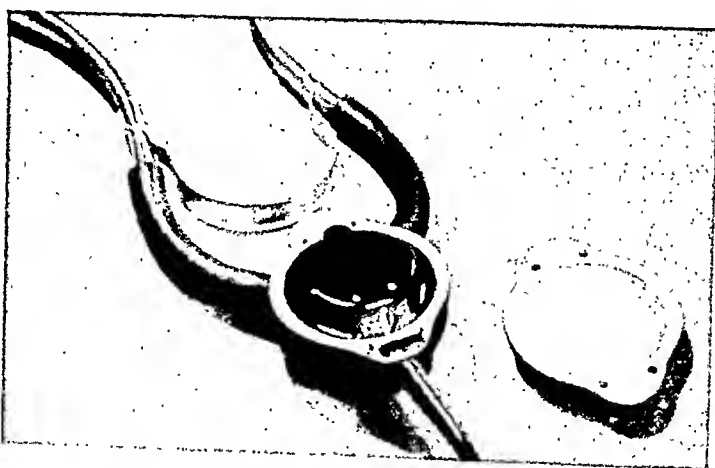


Fig. 16B.—Manner in which electromagnetic phone is inserted into audiophone.

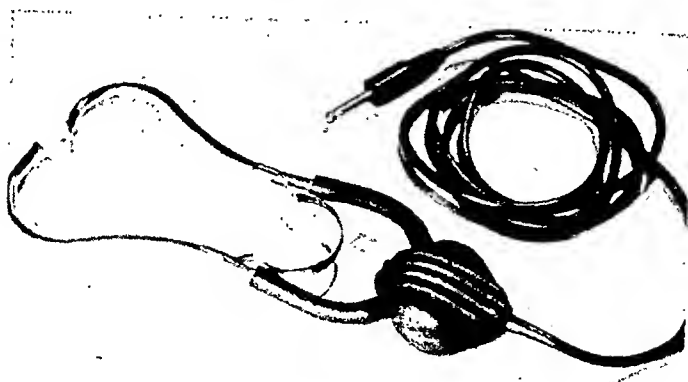


Fig. 16C.—Assembled audiophone.

capacitance to the audiophone, the ratio of the pressure developed in the ear cavity to the amplitude of the diaphragm vibrations should be independent of the frequency.

An interesting point is that the impedance offered by the ear cavity to the audiophone at the higher frequencies is not purely capacitive, but becomes more so at the lower frequencies. This phenomenon is caused by the presence of standing wave systems between the transducer and portions of the ear cavity, as well as by absorption effects which may be considered equivalent to a resistive component. This effect is of small consequence in auscultatory work, for the frequencies which are encountered do not exceed 1,000 cycles per second. On the other hand, at low frequencies, leakage which may occur in an improperly designed audiophone will give rise to a reactive and resistive component. This factor may vary from person to person if the ear pieces of the binaural are not properly placed. It is an important consideration in the action of the acoustic, as well as the amplifying, type of stethoscope. An hermetically sealed audiophone also eliminates room noises which seem greatly exaggerated; the same holds true for the acoustic stethoscope.

*The Amplifier.*—The stethograph-electrocardiograph amplifier (Fig. 17) comprises two amplifier channels of entirely independent and different electrical characteristics. One channel possesses electrical characteristics which are useful for amplifying the heart and chest sounds, whereas the other channel is suitable for amplifying the electrical heart action potentials which are encountered in electrocardiography.

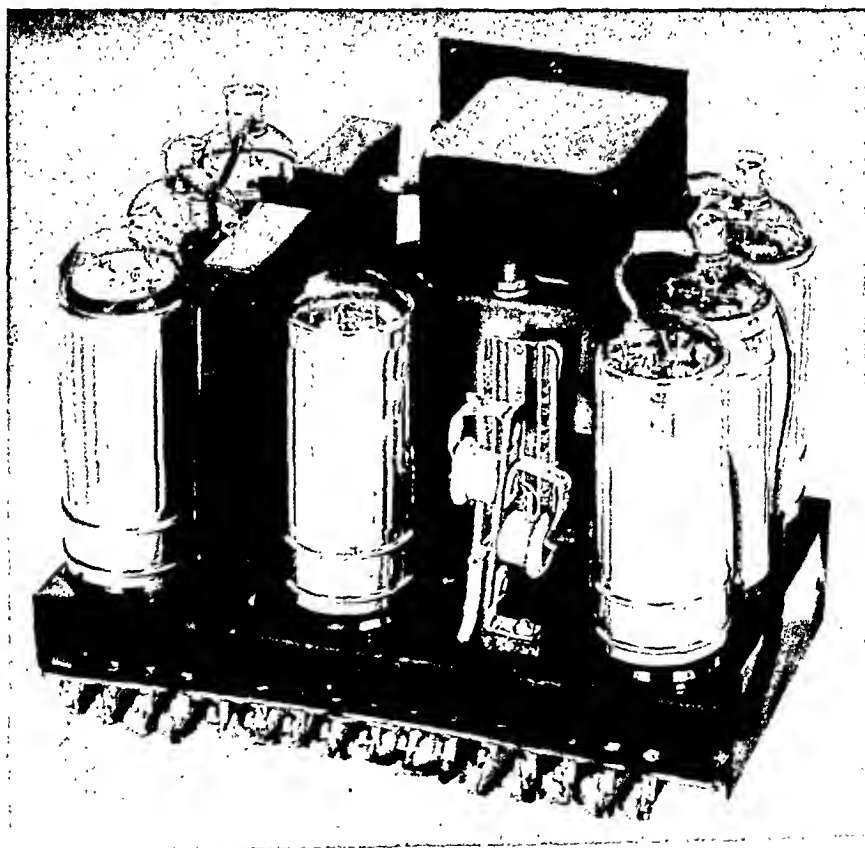


Fig. 17.—The stethograph-cardiograph amplifier.

The amplifier systems of the electrocardiograph-stethograph employ thermionic vacuum tubes. A thermionic vacuum tube consists of an evacuated enclosure containing a number of electrodes between two or more of which conduction of electricity through the vacuum may take place. The three most essential electrodes in a thermionic vacuum tube which is suitable for amplification purposes are the cathode, grid, and plate.





standards to follow; this is certainly a unique situation when we consider the importance of correct design in an instrument which is so widely used.

The primary requirements for any kind of stethoscope which is to be used by a competent observer with normal hearing are as follows:

1. The stethoscope must be capable of transferring all of the sounds from the patient to the observer's ear.
2. The transferred sounds must possess a quality or pitch of such a character as to be familiar to the observer.
3. The stethoscope must possess a means of attenuating certain portions of the auscultatory frequency band, in order to reduce masking effects.

In order to obtain a starting point in the effort to ascertain the optimal frequency response of a stethoscope, a study was made of the acoustic stethoscopes which are on the market. They were found to vary in tonal quality, and, in addition, the various commercially available chest pieces introduced different tonal qualities, as well as variations in intensity.

The next step was to investigate the nature of the two most commonly used chest pieces, namely, (1) the open bell, with a diameter of 1 inch, and (2) the "Bowles," or diaphragm type, with a working diameter of  $1\frac{3}{8}$  inches.

There was a slight variation in tonal quality and intensity when the most commonly used stethoscopes which employ these two chest pieces were compared. The general consensus of cardiologists was that, although a noticeable difference in tonal quality existed, it was insufficient to affect the general auscultatory technique.

Frequency response characteristic curves were obtained for the various popular makes of stethoscopes which employ the two chest pieces, and a mean frequency response characteristic was calculated. With this average curve as a basis, we constructed an amplifying stethoscope with a frequency response characteristic which was identical with the theoretically average stethoscope.

Fig. 18 is a schematic diagram of the apparatus employed in ascertaining the frequency response from which the mean stethoscope response characteristic was calculated. The characteristics of the loud speaker, the transmissional effects of the media comprising the patient's chest, and other such modifying factors were eliminated by the subtraction method (previously described in connection with the determination of the characteristic curves of the chest pieces of Fig. 5). A theoretical amplifying stethoscope frequency response curve, not including the modifying effects of the chest pieces which are capable of reproducing the sounds as they are heard with the theoretically average, acoustic stethoscope, is shown in Fig. 19. The construction of an amplifying stethoscope which has a frequency response characteristic identical with the theoretical one of Fig. 19 is quite practical, and this feature has been incorporated in the apparatus. It is well to mention that a slight variation in the slope of the curve below 200 cycles per second is sufficient

to alter considerably the quality of the sounds as they are heard with the amplifying stethoscope. A variation of considerable degree in the slope of the curve above about 200 cycles per second produces little effect upon the quality of the sound.

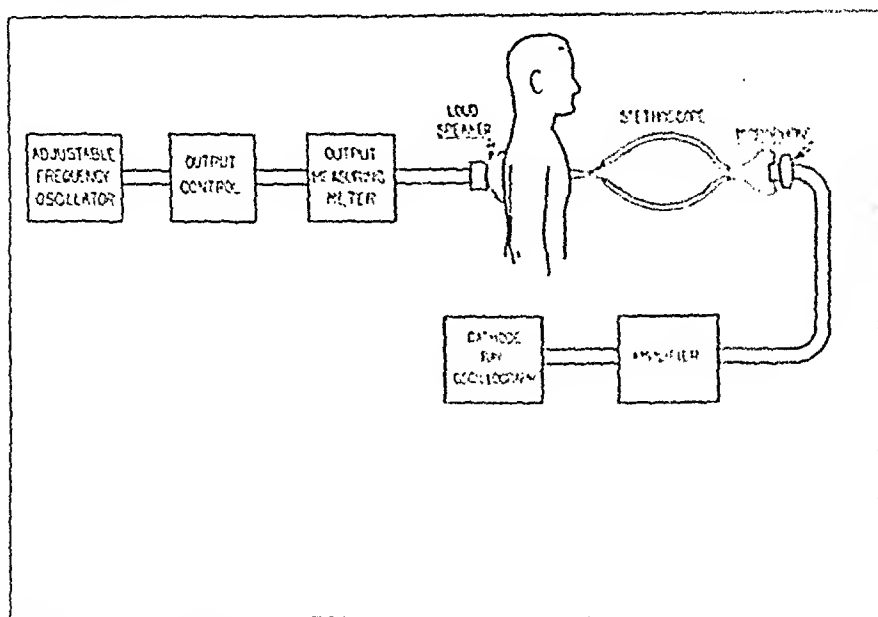


Fig. 18.—Schematic diagram of apparatus for comparing frequency response characteristics of acoustic stethoscopes and amplifying stethoscopes.

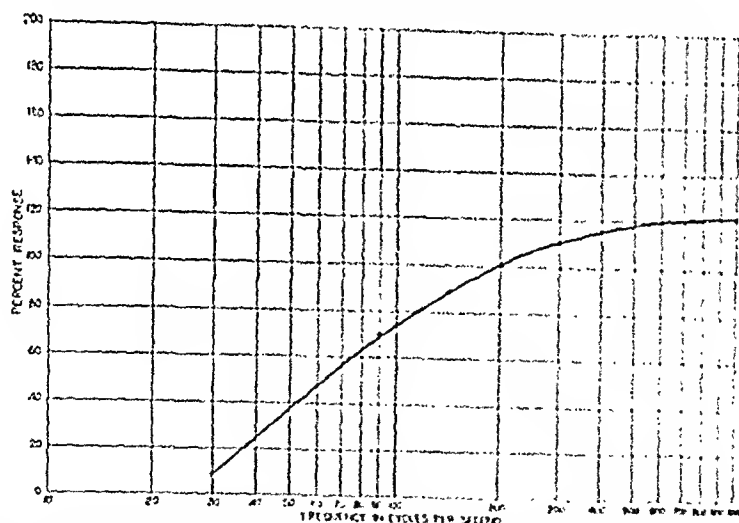


Fig. 19.—Output of amplifying stethoscope vs. input to microphone, omitting characteristics of chest piece. Ordinate plotted in per cent response instead of decibels, to accentuate graphically the degree of slope.

An amplifying stethoscope with a frequency response curve which is flatter below 200 cycles per second than the graph of Fig. 19 has a tendency to convey the sounds to the observer's ear (especially the low-pitched mitral diastolic murmurs) with a raspy effect. This foreign quality is so different from what is normally heard with the acoustic stethoscope that, at times, the observer has the feeling that the time he spent in perfecting his auscultatory technique was wasted, unless he

keeps going back to the acoustic stethoscope. This has been the major difficulty with electrical stethoscopes; it is no fault of the system, but of the basic design of the apparatus. *The low-pitched, raspy effect is more common in the electrical type of stethoscope than in the acoustic variety because it is easy to accentuate low-pitched sounds with an amplifying system, whereas, in the acoustic stethoscope, the low pitches are limited in relative intensity by the physical nature of the apparatus.*

*Effects of Sound Intensity Variation.*—Earlier in this paper it was shown that the average ear is most sensitive to variations in intensity above 50 decibels and gradually becomes less sensitive at the lower sensation levels. This is important in auscultation, for the intensity level is usually 10 decibels, or less, and the frequency band which is involved is at the lower extremity of the human hearing range. It is well to repeat that, with a frequency of 60 cycles per second, an intensity variation of 20 per cent is just perceptible when the sound level is 50 decibels, and a variation of as much as 200 to 300 per cent is necessary when the intensity level is 10 decibels.

Although a higher sensation level requires less of a frequency change for minimum perception, the ability of the ear to detect changes in frequency at the lower levels of intensity is not as poor as its ability to perceive intensity variations.

It has also been pointed out that the intensity of the sounds bears an important relationship to masking, pitch, etc. Stevens and Davis,<sup>23</sup> in their discussion of this phase of hearing, state:

“It has been the traditional view of psychology that the attributes of sensation show a one-to-one correspondence to the dimensions of the stimulus. Some such view is also implicit in the naïve epistemology of the physicist. He tends to think of pitch as if it were the perception of the frequency of a tone, but we have seen that holders of that view run into difficulties. The pitch of a pure tone can be altered without changing its frequency; likewise, the loudness of a tone may be varied without changing its intensity. Pitch is a function of two physical variables, frequency and intensity—loudness is a different function of the same two variables. Both pitch and loudness are fundamentally to be conceived as *reactions* on the part of organisms to sound waves. These are systematic reactions, to be sure, and can be ordered on scales and evaluated, but they are, nevertheless, products of the interaction of an atmospheric disturbance with a living system.”

The authors further state:

“Several writers, during the last century, have disclosed the fact that tones are characterized by an apparent ‘largeness’ or ‘extensiveness’ (Rich<sup>22</sup>). The low tones of an organ appear to be ‘bigger’ than the high chirp of a cricket, even when the loudnesses of the two are equal. This subjective aspect of a tone is known as volume. (The radio-engineer speaks of the ‘volume’ of a sound, or of the ‘volume control’ of a radio set, but he means by volume what we should properly call intensity.)”

In order to illustrate the manner in which these characteristics of hearing are related to auscultation, let us assume that a certain heart

lesion is present in an emaciated person, an obese person, a heavy, "barrel-chested" man, and a person with a chest of normal proportions. Let us further assume that the intensity, pitch, and quality of the heart sounds and murmurs are identical at the source in each case. Because of the different transmissional characteristics in these cases, the intensity of the sounds, as they are heard on the surface of the chest with the same acoustic stethoscope, varies decidedly. As a result of the intensity modification alone, sounds that are audible in the case of the normal and emaciated persons may not be heard at all when the stethoscope is applied to the obese and "barrel-chested" patients.

If the acoustic stethoscope employed in these cases had an adjustable intensity control, and the intensity levels were the same in all (i.e., approximately that of the sounds heard in the case of the patient with a normal chest), a considerable percentage of the distortion, or modification effects, would be eliminated. Also, certain possible masking effects could be reduced by slightly varying the intensity above or below that of the sounds heard over the normal chest; a noticeable variation in quality and pitch would also be apparent at the various hearing levels. Obviously, the acoustic stethoscope does not lend itself to adjustable intensity control, whereas the amplifying stethoscope is capable of such control.

*From this discussion it should be obvious that an amplifying stethoscope is not primarily an instrument to be used for making sounds many times louder than they can be heard with an acoustic stethoscope. The major advantage of the amplifying stethoscope over the acoustic stethoscope is that the intensity can be adjusted as desired, and thus a number of modifying characteristics which cannot be overcome with the acoustic stethoscope are eliminated. Roughly, the heart sound intensity in a normal young person, as perceived by auscultation with an acoustic stethoscope, is approximately optimal from a standpoint of masking, pitch, quality, and accustomed usage of the older acoustic stethoscope.*

Because of deviations of the individual physician's hearing from the "Average Normal Threshold Curves of Audibility and Feeling" (Fig. 1), it is obvious that, in any given case, the sounds heard by a group of trained observers, employing the same acoustic stethoscope, will not register identically, although the hearing of each may be considered normal. The most marked variations from normal would be found in the older observers, whose hearing is not so sensitive as that of the younger physician. A slight increase in the sensitivity of the stethoscope, to compensate for the decreased sensitivity of the ear, will bring back the keenness of hearing which is so necessary for maximum efficiency. Such compensation is at present impossible except with an amplifying stethoscope which has an adjustable and calibrated intensity control.

*Sound Filters.*—An acoustic or electrical filter system may be used with the electronic or electrical amplifying stethoscope as an aid in minimizing masking effects. Acoustic filtering is accomplished by means of the open and diaphragm chest pieces, which can be attached to the piezoelectric, crystal microphone. Electrical filtering is obtained by inserting "Campbell" filters, or any of the well-known modifications of the "Campbell" filter, between the microphone and the audiophone.

Dodge and Frederick,<sup>70</sup> of the Western Electric Company, first employed the "Campbell" filter in an amplifying stethoscope. The filter system was composed of a series of high-pass and low-pass filters. By means of a suitable switching system, any filter or combination of filters could be inserted into the amplifier circuit to allow any desired low frequency band, high frequency band, or intermediate frequency band to pass to the translating device. The amplifier proper had a frequency response characteristic that was flat over the auscultatory range.

From the physicist's point of view, the Dodge and Frederick system may be considered an excellent instrument for analyzing the frequency components of sounds. Williams and Dodge<sup>18</sup> and Cabot and Dodge<sup>22</sup> utilized the apparatus as an auscultatory wave analyzer, with noteworthy results. On the other hand, the clinical use of the apparatus was limited by the fact that it altered the quality of the sounds which are heard with the ordinary acoustic stethoscope. The modification of tonal quality introduced by the Dodge and Frederick apparatus was caused by the fact that its frequency response characteristic was different from that of the acoustic stethoscope. Furthermore, the sharp cutoff characteristics of the "Campbell" filters produced additional modifications of the sounds, although the sharper the cutoff the more suitable is the apparatus as a sound-wave analyzer.

In our opinion, for optimum clinical results, a stethoscope, whether it be electrical or acoustic, should possess a frequency response characteristic similar to that of the average commercial acoustic stethoscope, minus the modifying effect of the chest piece. The filters, whether they be electrical or acoustic, should possess modifying frequency response characteristics similar to those obtained with open bells of various diameters and diaphragm chest pieces made of plastic materials. In other words, the function of a filter in a stethoscope is not to eliminate a certain band of sound frequencies, but to alter the slope of the overall response of the basic curve, as shown in Fig. 19.

Heart and breath sounds are normally impure tones, or noises, and are therefore composed of a conglomeration of frequencies of multitudinous intensities. Each component frequency performs a distinct function, in that it imparts a distinguishing quality to the sound. Although a noise may sound high pitched, wave analysis usually shows that it comprises low, as well as high, frequencies, although the higher frequency components predominate. In cases in which the sounds appear to be low pitched, the reverse usually holds true.

To minimize the masking effects that a more intense and lower pitched sound may produce upon one of high pitch, as, for example, in the case of the aortic diastolic murmur of aortic insufficiency, an attenuating effect upon the lower frequency components would be a distinct ad-

vantage. For best results with the Dodge and Frederick system, using sharp cutoff, high-pass filters, the most suitable point of cutoff will depend upon the component frequencies of the sounds. Considerable variations in the relative proportion of high and low frequencies will be found in cases of aortic regurgitation. On the other hand, a filter such as the "Bowles" diaphragm chest piece, which progressively attenuates, but does not eliminate, the lower frequencies, is obviously less critical and more suitable for clinical use. A modified Dodge and Frederick filter system with a continuously adjustable cutoff filter may be employed. Confusion may arise with such a filter because of the difficulty of selecting and reproducing the optimum cutoff setting in routine clinical work.

Campbell filters, or their modifications, may be so designed that they reproduce the frequency response characteristics of open chest pieces of various sizes, as well as of diaphragm types; the lowest pitch chest piece is employed, and the auscultatory equivalents of the highest pitch chest pieces are obtained by inserting the equivalent electrical filter.

The choice between an acoustic filter and an electrical filter, therefore, reduces itself essentially to a question of economics and weight. Obviously, the acoustic filters are less costly and decidedly less massive. Also, the clinician is more familiar with the acoustic filter system.

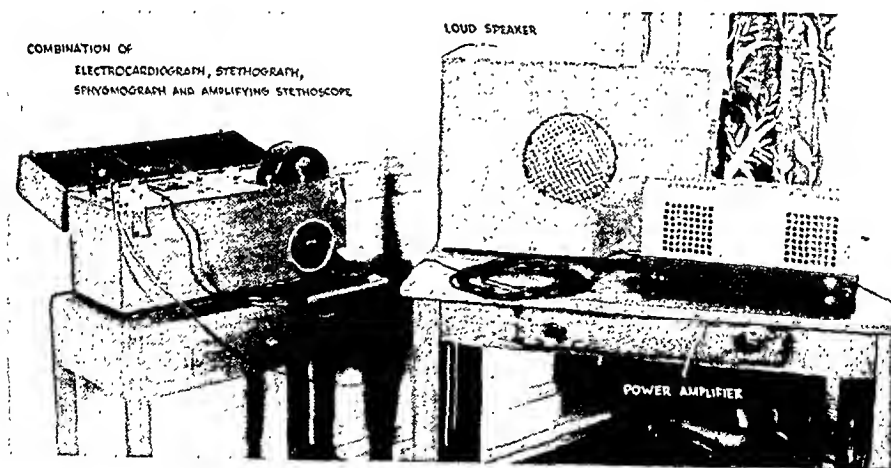


Fig. 20.—Stethograph-electrocardiograph with loud speaker attached.

*Applicable Electroacoustic Transducers.*—A loud-speaker system designed to operate with the amplifying stethoscope described in this paper is shown in Fig. 20. It is principally useful for teaching, although it has a few clinical applications. Several experimenters have constructed such units, but they have utterly failed to reproduce sounds of unmodified quality. The reasons for the previous failures are as follows:

A. The combinations of microphone and electronic amplification which were used did not possess a frequency response characteristic similar to that of the ordinary acoustic stethoscope.

B. The ordinary radio loud-speakers which were employed did not possess a frequency response characteristic suitable for clinical work.

C. Invariably, the power handling ability of the loud-speakers was insufficient to reproduce the heart sounds with sufficient intensity and with no overloading distortion.

The form of distortion that may be introduced by item A has been discussed previously; it will occur in a loud-speaker system, as well as in an amplifying stethoscope which employs an audiophone.

A loud-speaker which does not possess a frequency response characteristic over the auscultatory range similar to that of the audiophone previously described will alter the quality of the heart sounds. The average radio loud-speaker has a resonance peak in the vicinity of 100 cycles per second, or less. As a result, a booming character is imparted to the first and second heart sounds, producing a tom-tom drum effect. This drum effect, in addition to altering the quality of the heart sounds, decidedly masks any systolic and diastolic murmurs that may be present. The loud-speaker of Fig. 20 is totally free of resonance peaks in the auscultatory region.

We have found that a loud-speaker system must be capable of handling a minimum of 15 watts in order to reproduce the heart sounds without distortion in the average amphitheater or classroom. So much power seems unnecessary, on first thought. However, the large excursions of the loud-speaker diaphragm which are produced by the first and second heart sounds show that a large amount of power is being fed into the loud-speaker. The reason the diaphragm excursions do not produce terrifically loud sounds is that human hearing is very deficient in the frequency band of which these sounds are composed.

In order to deliver sufficient power to the loud-speaker, a power amplifier must be interposed between it and the amplifying stethoscope. The amplifier must not modify the over-all frequency response characteristic of the system.

Clinical tests showed that the loud-speaker system reproduced the heart sounds with a quality that was practically identical with that of the acoustic stethoscope. The efficiency of the acoustic stethoscope was somewhat better at the very low pitches, but the loud-speaker was excellent at the higher pitches. It was also noted that hearing efficiency improved for the very low pitches as the observer came closer to the loud speaker. The reason for this phenomenon is that, at the very low auscultatory frequencies, the sense of feel is more keen than the sense of hearing. A closed binaural conduction system increases the efficiency of feel for the low pitches, as compared to the efficiency of feel with a loud-speaker system.

A suitably designed bone conduction type of transducer may be used in place of the audiophone for the transformation of the amplified

electrical pulsations into sounds. The partially deaf physician whose hearing is more efficient by bone conduction than air conduction will obviously benefit by this arrangement.

*The Stethograph.*—Earlier in this paper, we described the manner in which the heart sounds are recorded graphically on sensitized photographic paper or film. The same electrical pulsations which pass to the audiophone are applied to the moving-coil galvanometer and are recorded photographically. Thus, an identical and known relationship exists between the sounds as heard and recorded.

*The Sphygmograph.*—A simultaneously registered stethogram and electrocardiogram, in certain cases, may not supply sufficient information for a complete analysis of all the events of the cardiac cycle. An additional simultaneous recording of a sphygmogram and stethogram, or all three together, must be resorted to. If two of the curves are recorded at the same time, the three may be correlated. Orías and Brann-Menéndez,<sup>71</sup> who have done a considerable amount of work on the physiologic aspects and interpretation of stethograms, state:

“Investigators who persist in the belief that the electrocardiogram will give all the data necessary for the interpretation of phonocardiograms will find themselves seriously limited in their studies, and will not be in a position to make the fullest use of their results.”

The authors give as an illustrative example:

“Those workers who have relied on the electrocardiogram alone to localize and correlate the vibrations recorded in the phonocardiogram have been forced to make suppositions based on time intervals between the events in both records. For example, if a sound is produced 0.08 to 0.14 sec. after the beginning of the P wave, it can be assumed that it is connected with auricular contraction; but if the sound is produced in diastole before, or at the same time as, the P wave, all that can be said is that this sound is not connected with auricular contraction. But in which definite moment of diastole is it produced? What is its probable cause? These questions cannot be answered.”

Ohm,<sup>72, 73</sup> Groedel,<sup>74</sup> Weber,<sup>75</sup> and Wolferth and Margolis<sup>77-79</sup> also recommend the addition of the phlebogram as a reference tracing.

In general, a tracing of the venous pulse is most useful in the study of the stethogram, for the following reasons:

- A. It may be recorded without any undue effort.
- B. The delay in the venous pulse when it is recorded at the lower portion of the neck is short and very nearly constant.
- C. The venous pulse portrays with good definition the various phases of the cardiac cycle and is an expression of the mechanical activity of the heart which produces the heart sounds.

Although it has been known for several centuries that there are venous pulses, they were not satisfactorily recorded until 1866, by Friedreich.<sup>76</sup> In 1893, Maekenzie,<sup>77, 78</sup> stimulated by a curiosity concerning the possible clinical significance of phlebograms, launched



a series of investigations which produced many enlightening physiologic facts.

The early sphygmographs employed purely mechanical recording systems, with necessarily massive levers and large friction styluses and pens. Wiggers,<sup>24a</sup> in his discussion of the mechanical recording type of polygraph, states:

"In order to render these systems sufficiently sensitive a considerable magnification of the lever is always necessary. In writing as they do, on horizontal surfaces, considerable friction between the writing point and the lever is, moreover, introduced. When, in addition, and contrary to all principles of good lever construction, a considerable weight is placed at the tip in order to enable these levers to record with ink, it can only follow that the instruments are inaccurate: (a) because they have a very slow inherent frequency; (b) because the curves are modified by friction on the drum; and (c) because, being periodic, they introduce lever vibrations which are frequently interpreted as waves of the venous pulse."

Dr. Wiggers obtained the following figures on some of the commonly used sphygmographs:

"Tambours of the Maekenzie ink polygraph have an inherent frequency of 4.5 per second, that of the Zimmermann polygraph, 5.8 per second, while the Jaquet polygraph heads the list with a vibration frequency of 6.5 per second."

In recent years, sphygmographie recording capsules which operate on optical and photosensitive principles have superseded the more sluggish mechanical systems. The Frank<sup>79-82</sup> segment capsule, which employs a beam of light produced by a suitable optical system, instead of a massive mechanical lever and stylus or pen, has been found most satisfactory and has been widely used. The beam of light has no weight, and therefore its movements are not modified or impeded by inertia and friction. Almost any desired degree of optical magnification of the pulse is obtainable, although the magnification is more or less limited by the intensity of the source of light and the necessity of obtaining good photographic definition.

The limiting characteristics of the Frank capsule sphygmograph are as follows:

A. The membrane is a thin rubber dam, to which a small, trapezoidal, celluloid plate is cemented. On the celluloid, in turn, is cemented a tiny mirror which pivots when the rubber diaphragm is excited. The capsule depends upon air damping, and thus a capsule of only a certain natural period will be critically damped. A capsule with a higher natural period will allow overshooting, and superimpose extraneous vibrations upon the sphygmogram, whereas one with a lower natural period will be overdamped and sluggish. As a result, only a critically damped capsule can be used when accurate sphygmograms are desired. It is not a very simple matter to produce critically damped capsules in commercial quantities.

B. The sensitivity of the Frank capsule type of sphygmograph may be controlled by either modifying the length of throw of the recording light beam or substituting capsules with celluloid plates of different trapezoidal shapes. When the optical throw is varied, the sensitivity is increased or decreased in a direct ratio. An elaborate laboratory setup, with an adjustable camera, permits modifications of the optical throw, but this is rather awkward in clinical work. Alterations in the length of the optical beam change the exposure intensity on the photographic paper and the width and photographic sharpness of the recording beam. Substituting capsules with celluloid plates of various trapezoidal shapes in order to obtain the necessary sensitivity is not very practical clinically, for such substitutions take time and require delicate adjustments of the optical system.

C. The life of the Frank capsule is short because the thin rubber dam deteriorates.

In order to overcome the imperfections of the mechanical and optical capsule types of sphygmographs, a piezoelectric system was devised to operate with the stethograph-electrocardiograph. Fig. 21 is a photograph of the sphygmographic unit,<sup>2</sup> which, when substituted for the patient in the electrocardiographic section of the stethograph-electrocardiograph, will record the sphygmogram.

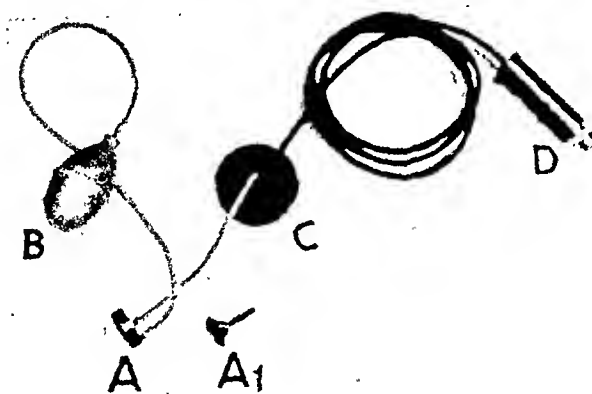


Fig. 21.—Piezoelectric sphygmographic attachment. A, Vacuum type applicator cup; A<sub>1</sub>, pressure type applicator cup; B, rubber bulb to produce vacuum in suction compartment of vacuum type applicator cup; C, piezoelectric microphone; D, cord and removable connector which fits into patient-cable receptacle of the electrocardiographic section of the instrument.

The attachment sphygmographic unit is composed of A, a vacuum type of applicator cup; A<sub>1</sub>, an alternate pressure type of applicator cup; B, a rubber bulb to produce a vacuum in the suction compartment of the vacuum applicator cup; C, a piezoelectric transducer; D, a cord and removable connector which fits into a patient-cable receptacle located on the control panel of the stethograph-electrocardiograph.

The vacuum applicator cup consists of a double chamber. The inner chamber is used for picking up the arterial or venous pulsations, whereas the outer chamber, which is connected to bulb B through rubber tubing, serves as a suction chamber for fastening the cup to the patient. A pressure type of funnel-shaped applicator (A<sub>1</sub>) may be substituted when desired.

The pulse sets up air pressure changes in the applicator cup. The pressure changes are then transmitted through the rubber tubing to the piezoelectric transducer, which converts them into equivalent, minute, electrical pulsations which are, in turn, fed into the electrocardiograph amplifier and recorded like an electrocardiogram.

The piezoelectric transducer operates on a principle identical with that of the stethograph microphone and has a flat frequency response from practically zero to several hundred cycles per second.

The connector D is so wired that, when the electrocardiograph selector switch is set in the "Lead 1" position, the minute electrical pulsations produced by the piezoelectric transducer are intensified by the electrocardiograph amplifier and recorded photographically. The amplitude of the sphygmographic deflection is regulated by means of the electrocardiograph sensitivity control, and the recording beam is centered by means of the electrocardiograph beam-centering mechanism.

The following are some of the more important characteristics of a piezoelectric sphygmograph when it is used in conjunction with the electronic electrocardiograph:

<sup>2</sup>This instrument is to be described in a paper by Arthur Miller, Sc.D., and Paul D. White, M.D.

A. The speed of response is limited by the d'Arsonval galvanometer. The galvanometer employed in the electrocardiograph has a deflection time of approximately 0.01 second, as may be seen from the "straight line" graph in Fig. 22. The

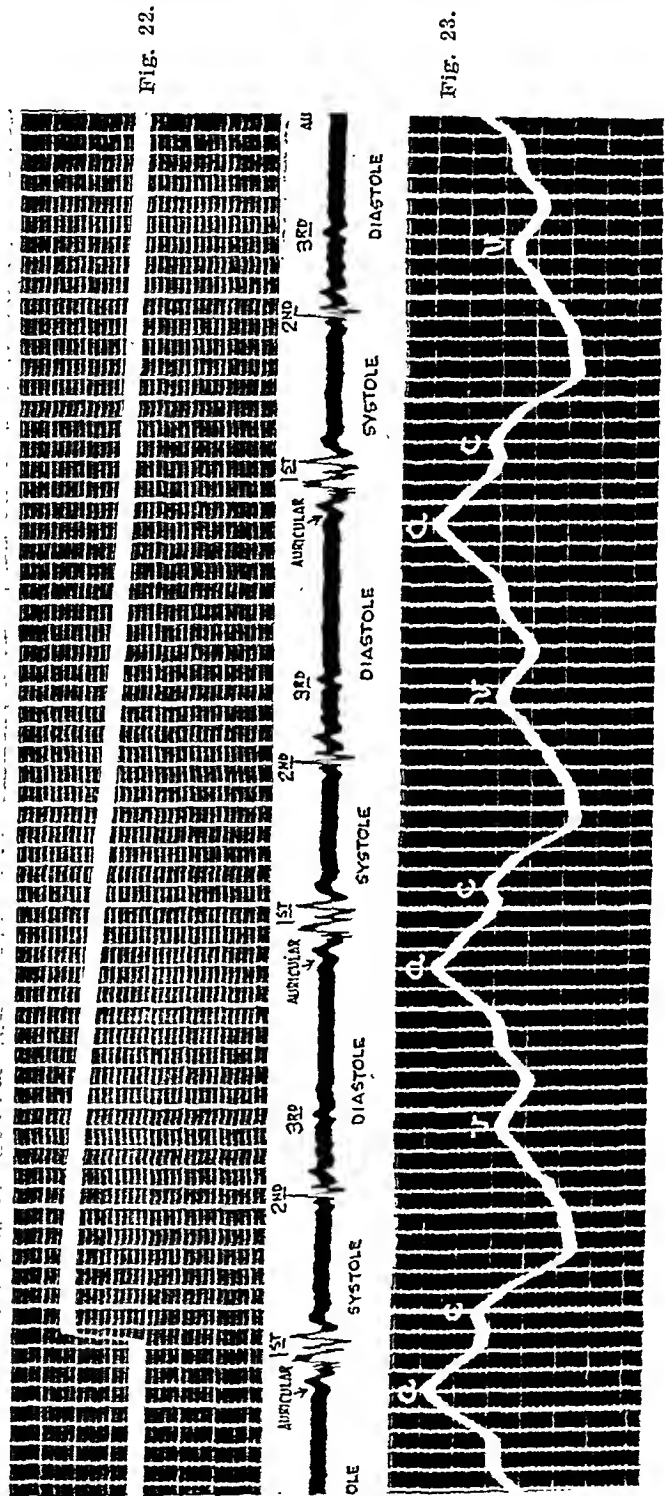


Fig. 22.—Response characteristic of electrocardiograph section.  
Fig. 23.—Simultaneously recorded stethogram and venous sphygmogram of a normal person.

"straight line" curve was obtained by applying a potential of 1 millivolt to the input of the amplifier. Each interval between adjacent vertical time lines is equal to exactly 0.04 second. A deflection time of 0.01 second is more than ample for sphygmographic and electrocardiographic purposes.

B. The logarithmic decay characteristic of the amplifier system is also illustrated by Fig. 22. For more than 0.2 second there is no decay whatsoever, and thereafter the decay is gradual. The 0.2 second during which there is no decay is certainly longer than the duration of any known electrocardiographic complex, and, inasmuch as the decay is slow after the 0.2 second, is ample for sphygmographic recording.

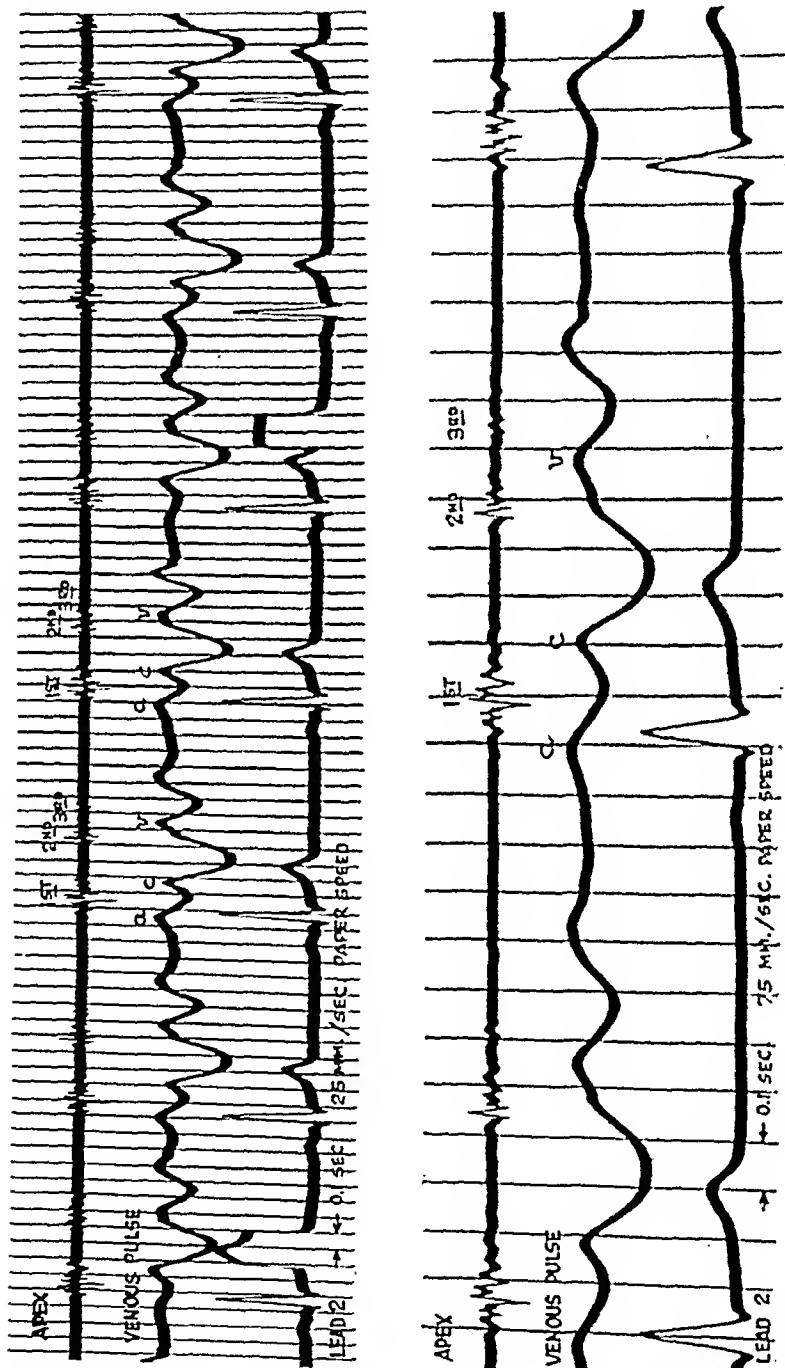


Fig. 21.—Simultaneously recorded stethogram (apex), venous sphygmogram, and electrocardiogram (Lead 2), at 25 and 75 millimeters per second camera speeds.

C. The electrical sensitivity control of the electrocardiograph is simple to use, and it does not alter any characteristic other than the sensitivity of the apparatus.

D. Once the recording beam is set, slight changes in the adjustment of the apparatus will not result in loss of the beam, for it gradually drifts into position because of the decay characteristic of the amplifier.

E. In the circuit there are no delicate parts which require protection.

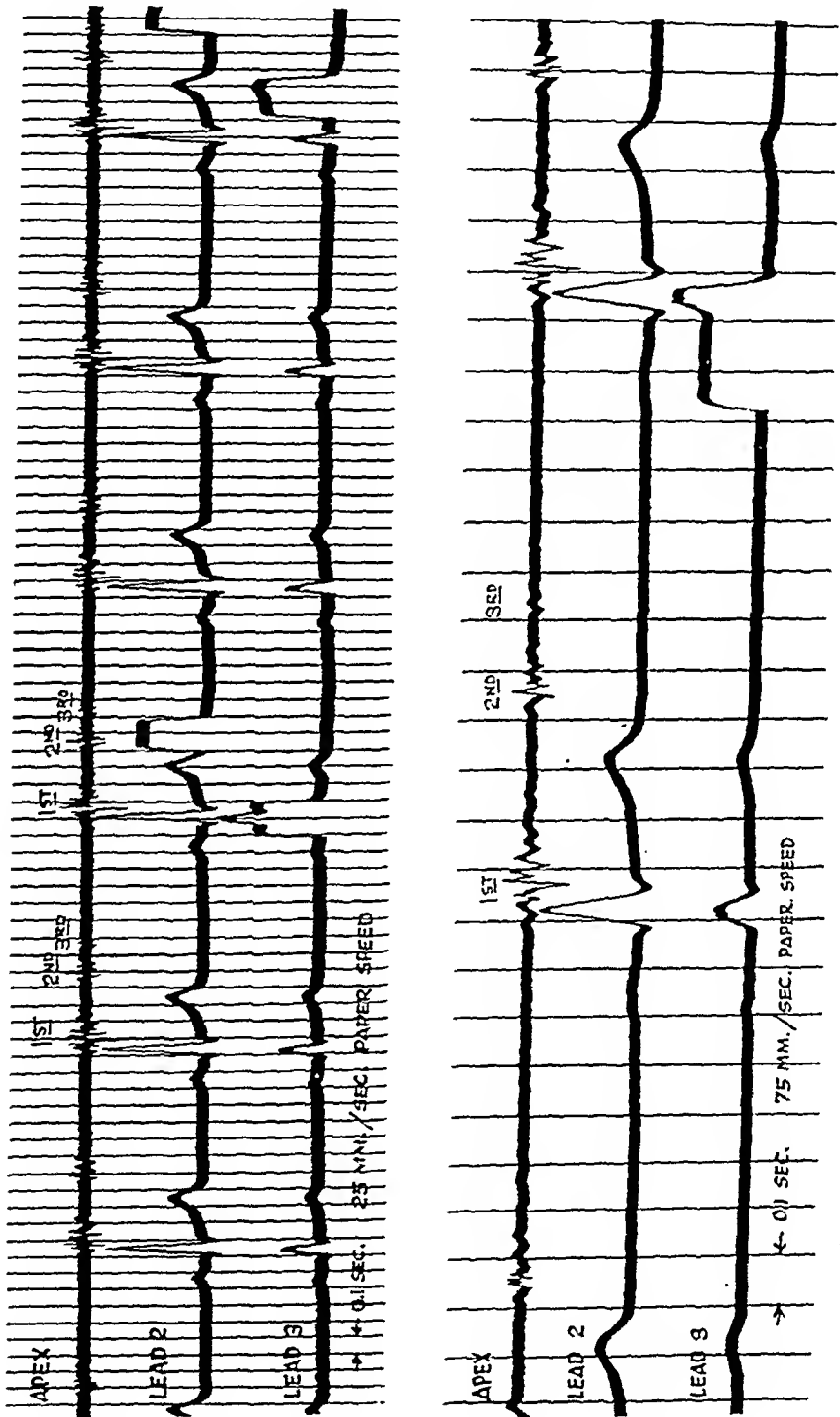


Fig. 25.—Stethogram (apex) taken simultaneously with electrocardiographic Leads 2 and 3.

Fig. 23 shows a venous pulse tracing which was taken simultaneously with the stethogram on a normal subject.

The addition of another electrocardiographic section to the stethograph-electrocardiograph permits registration of three simultaneous physiologic events. The

following combinations are thus made possible: (1) Stethogram, sphygmogram, and one electrocardiographic lead; (2) Stethogram and any two sphygmograms; (3) Stethogram and any two electrocardiographic leads.

When more than two registrations are made simultaneously, it is advisable to employ a white background and record in black, for this allows the three beams to cross each other. Fig. 24 shows a simultaneously recorded stethogram, venous sphygmogram, and electrocardiogram. Fig. 25 illustrates a simultaneously recorded stethogram and two electrocardiographic leads.

## VII. SUMMARY AND CONCLUSIONS

1. Tones of different periods of oscillation or frequency, but of similar intensity, affect the human ear to different degrees. The audiogram, which is a graphic representation of the threshold of audibility, is a measurement of the degree to which human hearing varies with respect to the frequency of vibration of the stimulus.

2. The minimum change in intensity of a sound stimulus to which the human ear is capable of responding varies with the general level of the sound, as well as with its frequency. In the auscultatory frequency band, as the frequency of the stimulus is lowered, a decidedly greater percentage variation in intensity is therefore required to produce the minimum perceptible change.

3. The human ear is a better detector of changes in frequency than of changes in intensity. A sound stimulus with a high sensation level requires less of a frequency variation to produce minimum susceptibility than does a sound stimulus of a lower sensation level. Also, the ear is somewhat less sensitive to frequency variations at the lower end of the auscultatory frequency band than it is to variations in the upper region.

4. In the auscultatory frequency band, the frequency of a stimulus may be varied rapidly over a considerable portion of an octave without detection by the ear.

5. The auditory sensation produced by a complex sound may be decidedly different in character, as well as in intensity, when the stimulating level is decreased or increased, even though no distortion is introduced. As a complex sound, such as a murmur, becomes more intense, the low-pitched components appear more prominent to the observer.

6. When a sound of comparatively high intensity immediately precedes a sound of considerably lower intensity, masking of the sound of lower intensity may result.

7. There are many paths along which heart and chest sounds travel in the human body in order to reach the surface. As a result, a large percentage of the sound energy never reaches the surface because of viscosity, elasticity, density, spreading, reflection, and refraction losses.

8. The entire auscultatory frequency band for heart sounds and murmurs lies below 1,000 cycles per second. An estimation of the lower frequency limit of heart sounds and murmur components puts it in the

vicinity of 5 to 10 cycles per second, although 30 to 40 cycles per second is the lower limit of audibility.

9. Acoustic stethoscopes may be classified as either monaural, binaural, or differential. Either the monaural or binaural stethoscope may be employed for general auscultatory purposes, whereas the differential stethoscopes are primarily instruments for localizing and comparing sounds.

10. The open stethoscopic chest piece, or bell, when applied to the patient's chest, may be considered as a diaphragm type of chest piece. The skin which is bounded by the lip of the bell forms the diaphragm, and the fleshy portion under the skin acts as a damping medium.

11. The larger the diameter of the open stethoscopic chest piece, the better its response to low-pitched sounds. This is accomplished at the expense of the higher frequency components.

12. The greater the pressure with which the open stethoscopic chest piece is applied to the patient's chest, the better is the response of the stethoscope to higher frequency components. Thus, by varying the application pressure, the physician exerts a variable filtering action upon the sounds because the natural period of the skin diaphragm bounded by the chest piece depends on the application pressure.

13. Open stethoscopic chest pieces of various geometrical shapes have been devised to improve the sound-accumulating efficiency of the stethoscope. A bell with its interior shaped like a parabola has been a favorite. Such chest pieces invariably decrease the efficiency of the stethoscope because they increase the internal volume of the chest piece.

14. The only important consideration when designing an open stethoscopic chest piece is to keep its internal volume at a minimum and have it so shaped that, in the case of an obese patient or one with an inelastic chest wall, the bell will not fill with flesh to such an extent as to decrease effectively the diameter of the enclosed diaphragm.

15. The diaphragm type of chest piece (Bowles type), which is commonly used in auscultation, is especially useful in detecting faint, high-pitched sounds. When it is applied to a patient's chest, the principle of operation of the Bowles chest piece is similar to that of the open bell, except that additional attenuation of the lower pitched heart and chest sound components is obtainable with the Bowles chest piece, and this prevents masking of the higher pitched components.

16. In the Bowles chest piece, as in the open type of chest piece, the air volume should be made as small as possible in order to obtain maximum efficiency.

17. Between 60 and 400 cycles per second, which includes most of the auscultatory region, tests show that the binaural method of auscultation through rubber tubes is, on an average, 20 decibels better than the monaural method, with the ear directly applied to the stethoscope. A 20-decibel difference is equivalent to a tenfold increase in sound pressure at the ear drum. Only between 850 and 1,000 cycles per second is





events of the cardiac cycle, particularly those which occur in diastole. For accurate analysis in such cases, a sphygmographic recording mechanism must be added to the apparatus, so that a simultaneous sphygmogram and stethogram may be taken to correlate with the simultaneous electrocardiogram and stethogram. A three-element recording system, capable of simultaneously recording the electrocardiogram, stethogram, and sphygmogram, eliminates the correlation procedure.

#### ADDENDUM

Since the completion of this paper, Johnston and Kline<sup>100</sup> have presented their data on the acoustic stethoscope. The testing procedure employed by these authors is significant, in that it is one of the first attempts at a quantitative analysis of stethoscope performance. A comparison of the data obtained by Johnston and Kline with our observations is of interest.

The experimental setup of Johnston and Kline was composed of: "A special telephone receiver, driven by a variable frequency oscillator, placed within the heart of a cadaver by means of an abdominal-diaphragmatic approach, so that vibrations of any desired amplitude and pitch were transmitted to the intact thoracic wall over the heart. The vibrations were picked up by the end pieces of the stethoscope and conveyed through the columns of air of the instrument to a condenser microphone. The output from the microphone was passed into a suitable vacuum-tube amplifier, and thence to an output meter of the rectifier type. The readings of this meter were proportional to the intensity of the sound waves striking the diaphragm of the condenser microphone. All tests were made with the end pieces of the stethoscope held rigidly against the same point on the precordium, and great care was taken to be sure that each end piece was in air-tight contact with the skin."

The Johnston and Kline calibration procedure was as follows: "Before any tests on stethoscope units were undertaken, attempts were made to standardize the vibrations transmitted to the wall of the chest, so that their amplitude would be constant over the entire range of frequencies employed. This problem proved to be difficult and was not solved to our satisfaction. We finally used a crystal vibration pick-up, fixed at the chosen point on the precordium, and determined the value of the resistance which would give the same response on the output meter at each frequency."

It is our opinion that the Johnston and Kline procedure for obtaining the over-all frequency response characteristic of an acoustic stethoscope gives only a very rough approximation, for two major reasons:

1. A stethoscope does not have similar frequency response characteristics when used on a cadaver and on a living person. The difference in frequency response characteristic is caused by a definite difference



sponse characteristic of the stethoscope and defeats, to a certain extent, the purpose of the Bowles diaphragm. The removal of the Bowles diaphragm produces a still further modification, in that it becomes a hybrid open chest piece.

Johnston and Kline conclude that: "Although rubber tubing of different lengths, diameters, and degrees of stiffness modifies transmission, largely because of resonance phenomena, the differences are relatively small, and the response of a stethoscope depends more on the choice of the end piece than on the nature of the tubes that are used." Our data differ considerably on these points.

Above about 150 cycles per second, tubing length is a very important factor in stethoscopic efficiency. According to our Fig. 9, there is a mean difference between the energy levels of 3-inch and 26-inch tubes of approximately 10 decibels, which is a pressure ratio of about 3 to 1, as applied to the ears. This means that above approximately 150 cycles per second the average hearing ability with 3-inch stethoscope tubes is roughly four times as great as with 26-inch tubes—certainly a significant amount!

Furthermore, tubing length does not materially modify the quality of sounds, whereas the diameter of the chest piece or Bowles diaphragm does affect the quality. Any variations in the stethoscope frequency response below about 200 cycles per second result in a decided alteration in sound quality; above 200 cycles per second very little alteration takes place. Stethoscope tubing produces little change in the frequency response curve below 200 cycles per second, whereas the chest piece modifies the slope considerably. Therefore, it is not correct to speak of efficiency versus tubing length and chest piece, unless the frequency response and its effects upon human hearing are taken into account; this Johnston and Kline have not done.

The effects of stethoscope resonance on efficiency are small compared to tubing length because the major resonance peaks do not exceed the mean by more than about 5 decibels, and the individual peaks cover but a small portion of the auscultatory band. Also, the location of the resonance peaks may vary as a result of differences in observer's ear cavity volume, leakage, variations in commercial tubing, etc.

In order to increase the efficiency of the stethoscope, Johnston and Kline advise a reduction in the diameter of the tubing. They do not consider the fact that there is an optimum diameter for maximum efficiency. When the diameter is decreased beyond a certain point, losses caused by frictional resistance offered to the air column exceed the gains obtained by volume reduction.

Johnston and Kline finally conclude as follows: "We do not advise all physicians to discard the stethoscope to which they are accustomed for one that may be acoustically superior, because, except for sounds

that are so faint as to be nearly inaudible, the loudness of sounds through the instrument is of no importance." This statement is true if we disregard the characteristics of human hearing, as Johnston and Kline have done, but, if we do consider these characteristics, it is not true. We have pointed out that the degree of masking, as well as the quality of the sounds, may be affected by the loudness level.

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# THE EFFECT OF RE-ESTABLISHMENT OF CIRCULATION IN COMPLETELY ISCHEMIC KIDNEYS UPON THE BLOOD PRESSURE OF CATS, DOGS, AND RATS

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IN 1938, Taquini<sup>1</sup> reported that, when the kidney of a dog is made completely ischemic, re-establishment of the renal circulation is followed by a rise in blood pressure. In a previous study,<sup>2</sup> it was found that the expected rise in blood pressure did not occur in rabbits following the termination of complete renal ischemia which had lasted four to six hours. At that time, the only way to account for the difference in the response of dogs and rabbits was to assume a species variation. Because of the negative response in rabbits, it seemed desirable to extend these observations to other animals; in this communication we are reporting the effects upon the blood pressure of re-establishment of the circulation of ischemic kidneys in cats, dogs, and rats.

## CATS

*Method.*—Ninety-five experiments were performed upon eighty-four animals. Under ether anesthesia, the abdomen was opened, and, following removal of the perirenal fat (to eliminate collateral circulation to the cortex) and stripping of the renal pedicle, a bulldog clamp was applied to the entire left or right renal pedicle. The abdominal cavity was closed and the animal was allowed to recover from the anesthetic. Three to eight hours later the cat was anesthetized with nembutal, given intraperitoneally; the carotid was cannulated, and the blood pressure was recorded on a moving drum in the usual manner. The abdomen was then reopened through the previous incision. Following the establishment of a constant blood pressure level, the bulldog clamp was quickly and carefully removed from the renal pedicle. Changes in the blood pressure were observed.

Six of the cats served for two experiments each; the first kidney was removed after the first experiment; the second experiment, utilizing the remaining kidney, usually took place one week after the first. Five other cats also served for two experiments each; bulldog clamps were placed on both renal pedicles of each animal during the first operation. Several hours later one clamp was removed, and, after the change in blood pressure had apparently run its course and the pressure had returned to or near the previous level, the other clamp was released and changes in blood pressure were observed.

After completion of this part of the experiment, the kidney whose pedicle had been clamped was tested to determine whether its circulation had been adequately restored following removal of the clamp. The following tests were employed:

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TABLE I

EFFECT OF RE-ESTABLISHMENT OF THE CIRCULATION OF COMPLETELY ISCHEMIC KIDNEYS OF CATS

ANIMAL NO.	PEDICLE CLAMPED	TIME CLAMPED (HOURS)	B.P. BEFORE REMOVAL OF CLAMP (MM. HG)	B.P. FOLLOWING REMOVAL OF CLAMP (MM. HG)	NET RISE IN B.P. (MM. HG)	STATE OF RENAL CIRCULATION
1	R	5	185	199	14	Good
2	R	6½	160	178	18	Good
3	R	5	192	212	20	Good
4	R	6½	166	166	0	Good
5	R	3	164	174	10	Good
6	R	5	136	162	26	Good
7	L	6	150	136	-14	Good
8	L	4	209	224	13	Good
9	L	4	186	206	20	Good
10	R	4	125	147	22	Good
11	R	4½	178	212	34	Good
12	L	5	142	170	28	Good
13	L	5	166	182	16	Good
14	R	5	162	179	17	Good
15	L	6	160	172	12	Good
16	L	4½	134	156	22	Good
17	R	4	144	148	4	Good
18	R	6	128	182	54	Good
19	L	4½	164	244	80	Good
20	L	4	144	180	36	Good
21	R	4	128	168	40	Good
22	L	4½	162	184	22	Good
23	L	5	140	176	36	Good
24	L	4	144	160	16	Good
25	R	4½	144	190	46	Good
26	L	4	140	114	-26	Good
27	L	5	160	124	-36	Fair
28	L	3	162	190	28	Good
29	R	3	185	199	14	Good
30	L	5	188	200	12	Good
31	L	5	178	220	42	Good
32	L	5	126	116	-10	Good
33	L	7	164	170	6	Good
34	L	5	156	162	6	Good
35	L	7	172	178	6	Good
36	L	4	195	199	4	Good
37	L	7	210	222	12	Good
38	L	8	166	218	52	Good
39	L	7	138	242	104	Good
40	L	5	156	174	18	Good
41	L	5	124	176	52	Good
42	L	5	144	184	40	Good
43	L	5	152	208	56	Good
44	L	5	188	216	28	Good
45	L	5	124	144	20	Good
46	L	5	70	136	66	Good
47	L	5	160	182	22	Good
48	L	3	174	212	38	Good
49	L	5	126	184	58	Good
50	L	5½	140	158	18	Good
51	L	5	140	230	90	Good
52	L	6	170	198	28	Good
53	L	5	148	188	40	Good
54	L	6	186	220	34	Good
55	L	7	156	180	24	Good
56	L	4	180	234	54	Good

TABLE I—CONT'D

ANIMAL NO.	PEDICLE CLAMPED	TIME CLAMPED (HOURS)	B.P. BEFORE REMOVAL OF CLAMP (MM. HG)	B.P. FOLLOWING REMOVAL OF CLAMP (MM. HG)	NET RISE IN B.P. (MM. HG)	STATE OF RENAL CIRCULATION
57	L	4½	154	196	42	Good
58	L	5½	178	192	14	Good
59	L	3½	76	132	56	Good
60	L	4½	186	224	38	Good
61	L	5	202	226	24	Good
62	L	4½	166	192	26	Good
63	L	4	206	214	8	Good
64	L	4	156	172	16	Good
65	L	4	174	260	86	Good
66	L	5½	192	206	14	Good
67	L	4	150	196	46	Good
68	L	5	166	226	60	Good
69	L	5	154	252	98	Good
70	L	4½	186	210	24	Good
71	R	3	182	206	24	Good
72	L	3	192	200	8	Good
73	L	5½	176	200	24	Good
74	L	3½	200	218	18	Good
75	R	5½	156	176	20	Good
76	L	7	144	186	42	Good
77	L	3½	122	148	26	Good
78	L	4½	178	196	18	Good
79	L	4½	172	206	34	Good
80	L	6	180	232	52	Good
81	L	4	172	252	80	Good
82	L	4	188	220	32	Good
83	L	5	176	224	48	Good
84	L	5½	158	180	22	Good
85	L	3½	182	218	36	Good
86	R	4	200	228	28	Good
87	L	4			28	Good
88	R	4			68	Good
89	L	3	108	146	38	Good
90	R	3	140	158	18	Good
91	L	4½	160	170	10	Good
92	R	4½	178	196	18	Good
93	L	5½	200	238	38	Good
94	R	5½	216	254	38	Good
95	R	3½	160	210	50	Good
Av.		5½			30.12	

(1) A dose of 0.025 mg. of epinephrine was injected into the substance of the kidney; an immediate rise in systemic blood pressure indicated that the renal circulation had been re-established.

(2) The cortex of the kidney was punctured with a pointed instrument; profuse bleeding demonstrated that the vessels were patent.

#### RESULTS

In eighty-three of the ninety-five experiments, re-establishment of the circulation in the completely ischemic kidney resulted in an elevation of the blood pressure of at least 10 mm. Hg; the average was 35 mm. Hg. In seven experiments the rise in blood pressure was less than 10 mm. Hg; in one experiment there was no rise in blood pressure; and in four experiments there was a fall. The average rise in blood pressure for all ninety-five experiments was 30.12 mm. Hg (Fig. 1, Table I).

The blood pressure usually began to rise five to thirty seconds after the removal of the clamp, reached its maximum after two to four minutes, and then gradually returned to its former level. Although no

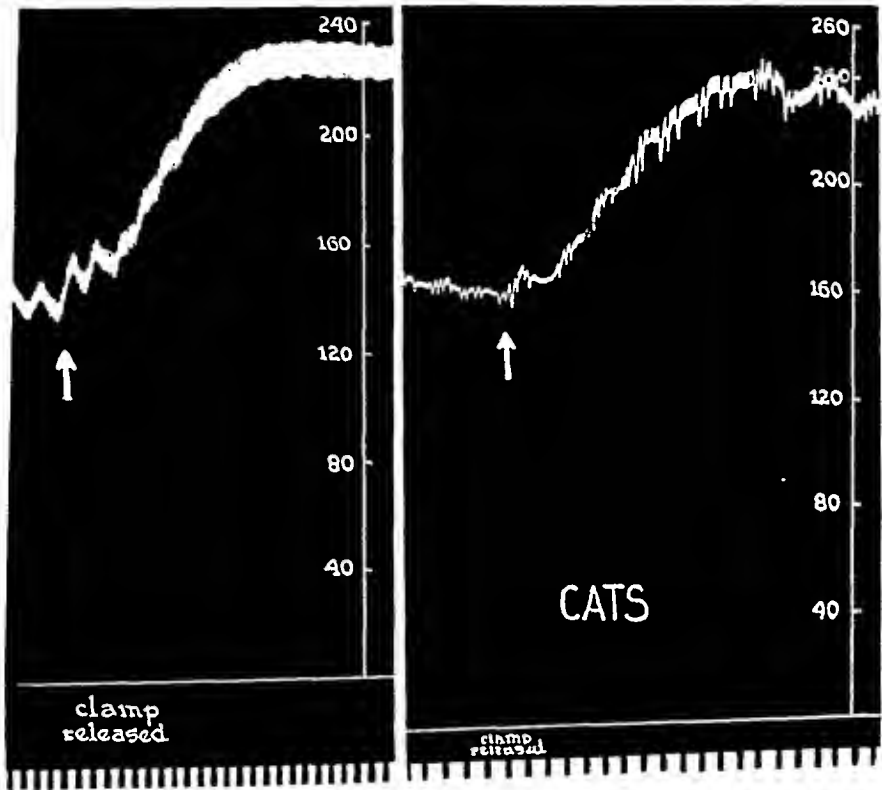


Fig. 1.—Kidneys completely ischemic for five hours. In each instance, clamp was removed at arrow, re-establishing circulation in the ischemic kidney. Nembutal anesthesia. Blood pressure in millimeters Hg. Time marker, fifteen seconds.

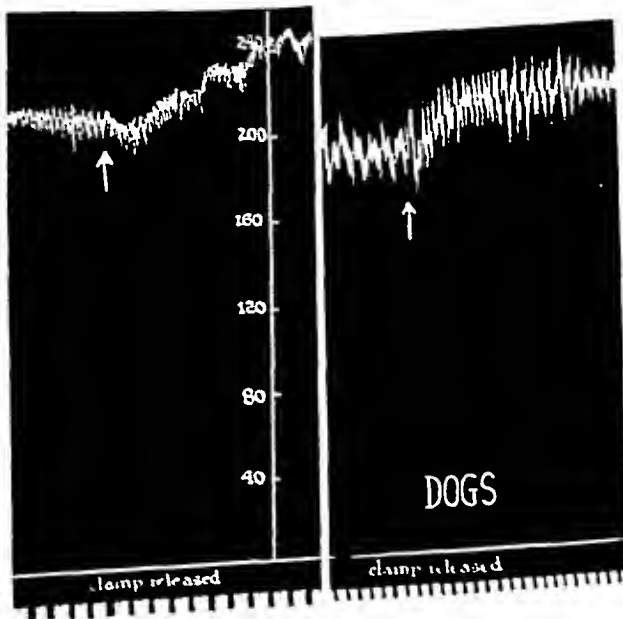


Fig. 2.—Kidneys completely ischemic for five hours. In each instance, clamp was removed at arrow, re-establishing circulation in the ischemic kidney. Nembutal anesthesia. Blood pressure in millimeters Hg. Time marker, fifteen seconds.

effort was made to correlate exactly the duration of the ischemia with the rise in blood pressure, there was no significant difference after varying periods of ischemia. It is likely that if intervals of less than three hours had been employed, a difference would have been apparent.

## DOGS

*Method.*—There were seven animals in this series. The technique was the same as that used on cats, except that all of the dogs were anesthetized by giving them nembutal intraperitoneally for the first as well as the second operation. Renal ischemia was maintained in this series for five to eight hours. The kidney circulation was tested as previously described for cats.

## RESULTS

In two of the seven experiments the renal circulation was not re-established, and these were discarded. A significant rise in blood pressure occurred in four of the remaining five animals; the average rise was 21.4 mm. Hg (Fig. 2, Table II).

TABLE II  
EFFECT OF RE-ESTABLISHMENT OF THE CIRCULATION OF COMPLETELY ISCHEMIC KIDNEYS OF DOGS

ANIMAL NO.	PEDICLE CLAMPED	TIME CLAMPED (HOURS)	B.P. BEFORE REMOVAL OF CLAMP (MM. Hg)	B.P. FOLLOWING REMOVAL OF CLAMP (MM. Hg)	NET RISE IN B.P. (MM. Hg)	STATE OF RENAL CIRCULATION
1	L	6½	135	155	20	Good
2	L	5½	210	248	38	Good
3	R	5½	172	174	2	Good
4	L	5½	182	199	17	Good
5	R	6	190	220	30	Good
Av.		6	177.8	199.2	21.4	

TABLE III  
EFFECT OF RE-ESTABLISHMENT OF THE CIRCULATION OF COMPLETELY ISCHEMIC KIDNEYS OF RATS

ANIMAL NO.	PEDICLE CLAMPED	TIME CLAMPED (HOURS)	B.P. BEFORE REMOVAL OF CLAMP (MM. Hg)	B.P. FOLLOWING REMOVAL OF CLAMP (MM. Hg)	NET RISE IN B.P. (MM. Hg)	STATE OF RENAL CIRCULATION
1	L	5½	136	160	24	Good
2	L	5	141	176	35	Good
3	L	6	144	182	38	Good
4	L	6½	136	215	79	Good
Av.		6	139	183	44	

## RATS

*Method.*—Four animals were anesthetized with ether. In each case the abdomen was opened through a midventral incision, the left kidney and its pedicle were carefully isolated, and a bulldog clamp was placed upon the pedicle. The abdomen was then closed, and the animal was allowed to recover from the anesthetic. Five to six and one-half hours later the rat was reanesthetized with nembutal, given intraperitoneally; the abdomen was reopened through the previous incision; the abdominal

aorta was cannulated with a three-way metal cannula; and the blood pressure was recorded on a moving drum. When a constant blood pressure level had been established, the clamp was removed from the renal pedicle and changes in blood pressure were observed. The state of the circulation in the kidney was tested by injection of epinephrine into the kidney substance and by puncture of the renal cortex, as previously described.

### RESULTS

There was a significant rise in blood pressure after removal of the clamp from the renal pedicle in every instance; the average rise was 44 mm. Hg (Fig. 3, Table III).

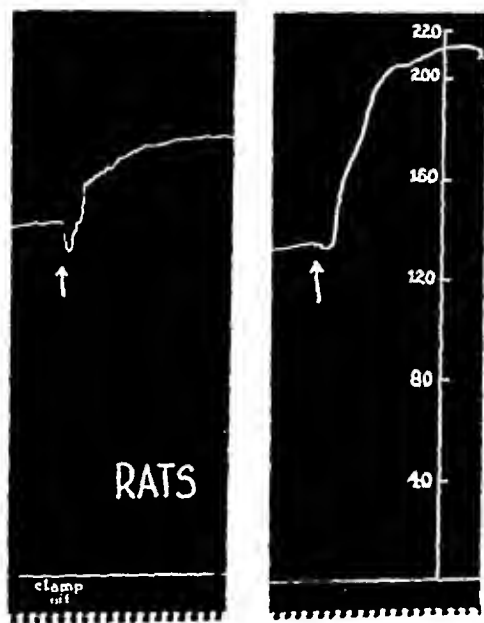


Fig. 3.—Kidneys completely ischemic for five hours. In each instance, clamp was removed at arrow, re-establishing circulation in the ischemic kidney. Nembutal anesthesia. Blood pressure in millimeters Hg. Time marker, fifteen seconds.

### DISCUSSION

These observations demonstrate that re-establishment of the circulation in the completely ischemic kidney in cats, dogs, and rats is followed by a rise in blood pressure. In previous communications<sup>3, 4</sup> it was shown that this rise is caused by the release into the general circulation of a pressor substance, probably renin or a closely related substance, which is produced in the ischemic kidney. It was also shown that the kidneys of rabbits which had been rendered completely ischemic for four to six hours fail, for some unexplained reason, to produce the pressor substance. This accounts for the fact that the blood pressure does not rise in rabbits.

### SUMMARY AND CONCLUSIONS

1. Complete renal ischemia was produced in ninety-five kidneys of eighty-four cats by clamping the renal pedicle. Following the re-

establishment of the circulation of the ischemic kidney, a significant rise in blood pressure occurred in eighty-three experiments.

2. The same experiment was performed on four rats and five dogs. A significant rise occurred in all but one of these experiments.

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# SOME PRINCIPLES GOVERNING THE SUPPLY OF BLOOD TO THE MYOCARDIUM IN OCCLUSIVE ARTERIAL DISEASE

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## INTRODUCTION

MANY anatomists since Lower<sup>1</sup> have called attention to the peculiar arrangement of the muscle fibers and bundles in the ventricles of mammalian hearts. At first these bundles were divided into superficial and deep layers, running in different directions. Gerdy,<sup>2</sup> Mall,<sup>3</sup> Flett,<sup>4</sup> Robb,<sup>5</sup> and others have attempted to define several muscle groups, which can be demonstrated consistently, and have given them the status of independent muscles. Four of these, the superficial bulbospiral, the superficial sinospiral, the deep bulbospiral, and the deep sinospiral muscles, are easily demonstrable anatomically, and sometimes another, the scroll muscle, can be separated.

Robb<sup>6</sup> has shown by experimental ligation of arterial branches of the coronary tree and by electrocardiographic studies that there is much evidence that these muscles function as correlated units.

The author showed, in 1939 (Lowe<sup>7, 8</sup>), that, under certain circumstances, naturally occurring pathologic processes, such as infarction and scar formation in the ventricular walls, follow the anatomic distribution of these muscle bundles. Recently, two additional instances in which the arrangement of pathologic processes depended on the anatomic distribution of the muscles in the ventricular wall have been recorded (Lowe<sup>9</sup>). In one case, petechiae resulting from acute leucemia occurred only in the superficial bulbospiral muscle; in the other, rupture of the left ventricle occurred, and the path of the escaping blood was in part determined by the muscle planes of the ventricular wall.

It may be assumed from this evidence, anatomic, physiologic, and pathologic, that the separate muscle bundles represent units of structure which constitute a physiologic, as well as an anatomic, entity.

In the investigations reported in this paper, colored gelatine masses were injected under carefully controlled pressures into the coronary circulation through both the main coronary arteries and their smaller branches. The results which were obtained show that it is possible by this means to inject the vessels in a single muscle.

These results also indicate that there is a general principle which governs the blood supply to cardiac muscles in the presence of occlusive arterial disease.

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## METHODS

The hearts were obtained several hours after death. A large cannula was tied into the aorta (*Ao.*, Fig. 1), and the coronary circulation was perfused with normal saline solution through the aorta. The pressure applied was always of the same order as the arterial blood pressure had been during life. After the vessels had been thoroughly washed out with saline solution, a small cannula was inserted into a branch of one of the coronary arteries and directed centrally. The pressure of the perfusing fluid at the cannula in this small branch was recorded on an open manometer.

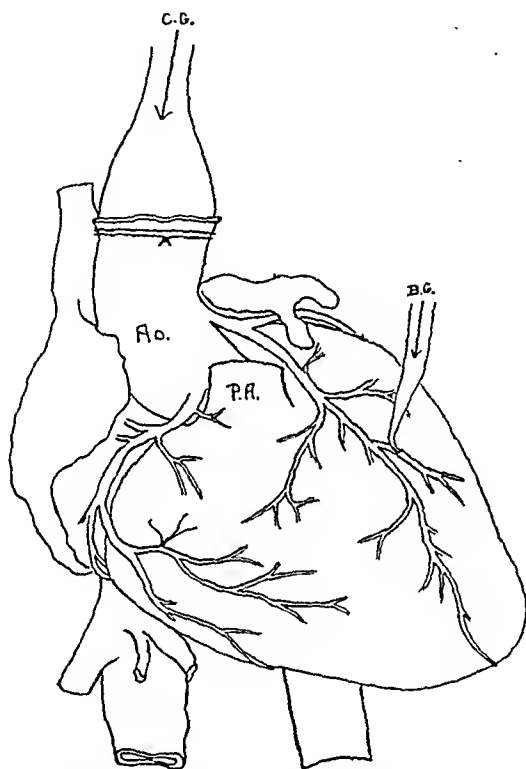


Fig. 1.—Drawing to illustrate injection experiments. Note cannulae in aorta (*Ao.*) and coronary branch, clear gelatine (*C. G.*) in aortic cannula, and blue gelatine (*B. G.*) in branch cannula. (Modified from Cloquet's Anatomy.)

After the pressure in the aorta and in the coronary branch had been recorded, the small cannula was reversed so that it pointed in a peripheral direction, and the branch was tied off proximally. A clear gelatine mass\* was then injected into the aortic cannula under various pressures. Simultaneously, a blue gelatine mass was injected into the branch cannula under a measured pressure which often corresponded to that recorded during the perfusion, but was capable of being raised or lowered at will (Fig. 1).

Throughout the whole experiment, all parts of the apparatus and the heart containing gelatine were kept immersed in a physiologic saline bath at a temperature of 37° C.

After the injection had been continued long enough to ensure that it was complete, the tubes to the cannulae were clamped while the gelatine was still under

\*The blue gelatine was prepared in the manner described in a previous paper (Lowe<sup>10</sup>). The clear gelatine was made in the same way but no pigment was added; the viscosity was subsequently adjusted by the addition of distilled water and checked in a viscometer.



pressure, and the heart and cannulae were immersed in cold, 10 per cent formalin solution. After twenty-four hours' fixation, the heart was cut into transverse slices about 2 cm. thick and fixed for an additional twenty-four hours. The pieces were then kept in hydrogen peroxide solution until the muscle was completely bleached.

From these sections, drawings showing the extent of the injections were prepared in a manner similar to that previously described (Lower).

#### SPECIMENS

*Specimen No. 67.\**—This was an adult heart into which a clear gelatine mass was injected through the aorta, and blue gelatine through a branch of the left circumflex coronary artery. The injection pressure was 180 mm. Hg in each case.

Examination of the sections showed a wedge-shaped area of injection extending from the pericardium to the endocardium in the posterior portion of the lateral wall of the left ventricle. The injected area also extended from the site of the injection (A, left middle section, Fig. 2) to the apex of the heart. There was no sign of laminar injection of the ventricular muscle, except in the section nearest the apex.

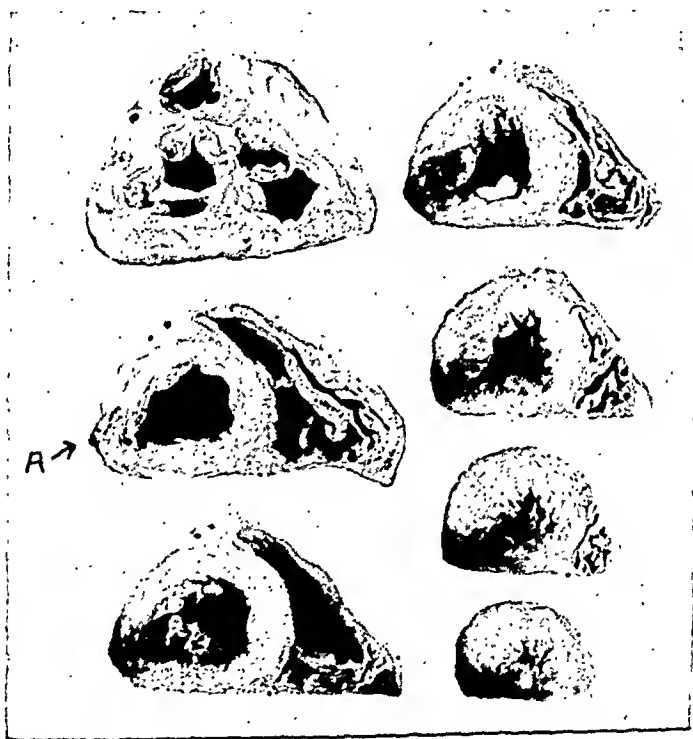


Fig. 2.—Photograph of the sections of an injected heart (Specimen 67), showing wedge-shaped, dark, injection areas in most sections.

*Specimen No. 69.*—This specimen was obtained from an adult with generalized atheromatous changes in the arteries. The pressures pertaining to the coronary arteries and aorta were ascertained by perfusion before the injection of the gelatine masses. A pressure of 190 mm. Hg in the aorta (clear gelatine) was combined with a pressure of 50 mm. Hg in the first branch of the anterior descending coronary artery, into which a blue gelatine mass was injected. After fixation, the heart was cut into the usual transverse slices.

When the sections were examined, a laminar scar was seen in the wall of the left ventricle, extending from near the base of the ventricles to near the apex

\*The specimen numbers refer to hearts which were examined in this and other investigations.

(Fig. 3a). Its greatest lateral extent was at a point about halfway between the base and apex, where it extended backward from the anterior edge of the lateral wall for approximately one quarter of the circumference. Above and below this region it gradually became narrower. At the point of its greatest thickness, the scar involved 80 per cent of the thickness of the wall of the left ventricle and was separated from the endocardial surface by a layer of muscle 1 or 2 mm. thick. Above this point the scar was dense, but, below it, it became less well defined and was interlaced with muscle bands.

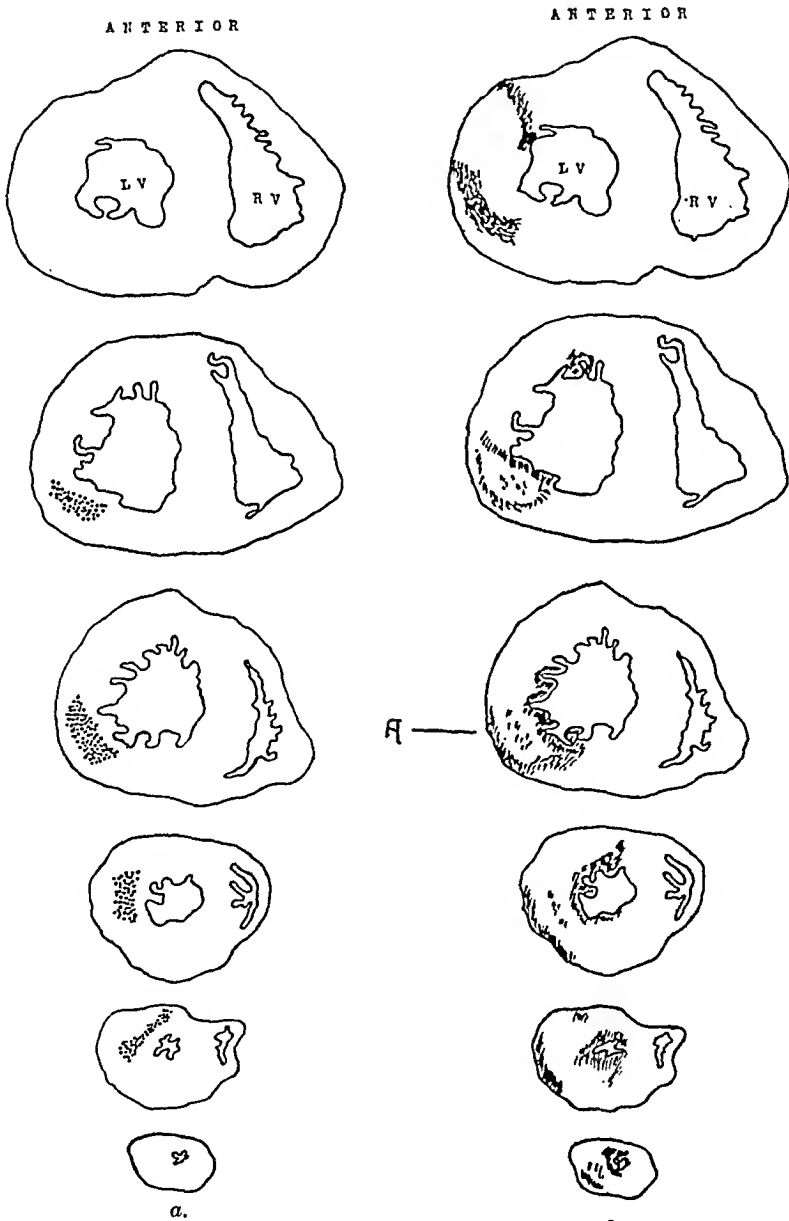


Fig. 3.—Drawings showing extent of scar (dotted areas, 3a) and injected areas (shaded areas, 3b) in Specimen 69. (Both diagrams on the same outlines, and may be superimposed.)

The blue gelatine mass extended up and down the ventricular muscle in laminae, and, in addition, some of it penetrated the papillary muscles and the scar tissue.

Some blue mass was also seen in the coronary artery above the point of injection (A, Fig. 3b); apparently, it had passed through collateral branches.

One of the laminae of blue mass was on the pericardial aspect of the ventricular muscle; it was a few millimeters thick and occupied a lateral position, as illustrated in Fig. 3b. Running from base to apex, it united at the apex with the other lamina, which was subendocardial and in the papillary muscles. This lamina stopped short of the base by about one-eighth of the distance from apex to base. In addition to these two laminae, there was some blue dye in the scar tissue. At the level of the injection of the blue mass (A, Fig. 3b) a wedge-shaped area of this mass extended through the whole thickness of the ventricular wall.

*Specimen No. 70.*—This preparation was obtained by injecting gelatine masses into a heart from a 14-year-old child. One cannula was inserted into the aorta and another into the first branch of the anterior descending coronary artery, a short distance from the junction with its parent vessel.

The pressures recorded during the preliminary perfusion were 120 mm. Hg in the aorta and 80 mm. Hg in this particular branch.

The injection was started with a pressure of 60 mm. Hg on the blue mass and no pressure on the clear gelatine in the aorta, and the blue mass ran easily into the coronary vessels distal to the cannula. However, when the pressure on the clear mass in the aorta was raised to 120 mm. Hg, the blue mass was forced back up the cannula until none could be seen in the coronary vessels. It was necessary to raise the pressure on the blue mass to 80 mm. Hg in order to obtain any flow into the coronary vessels against the pressure of the clear gelatine coming through the collateral circulation. By raising and lowering the pressures appropriately, it was possible to move blue gelatine up and down the vessels at will.

Finally, an injection was made with a pressure of 120 mm. Hg on the clear, and 80 mm. Hg on the blue, mass. The heart was then fixed, sectioned, and examined in the usual manner.

Near the site of injection, the blue mass had filled the capillaries in a wedge-shaped fashion from pericardium to endocardium (A, Fig. 4). As the sections were followed towards the apex, the injected area formed two laminae. One lamina was subpericardial; the other, subendocardial. At the apex these two laminae joined (lowest drawing, Fig. 4). Above the site of injection (A, Fig. 4) there was some injection of the ventricular muscle which was at first limited to the wedge shape, but nearer the base it assumed a laminal form. The whole of the injected region was on the lateral and posterior aspect of the left ventricle.

*Specimen No. 71.*—This heart was obtained from an adult who had had a systolic blood pressure of 220 mm. Hg and had died from cerebral hemorrhage.

Blue gelatine was injected into the first branch of the anterior descending coronary artery in accordance with the technique described. The pressures employed were the same as those applied previously during perfusion, i.e., 220 mm. Hg on the clear gelatine in the aorta, and 150 mm. Hg on the blue mass in the first branch of the anterior descending coronary artery.

After fixation, the heart was cut and examined. The injection in the region of the cannula extended throughout the whole wall in a wedge shape (A, Fig. 5). It extended in a superficial lamina from this point toward the apex, where it fused with a subendocardial lamina. There was also some injection of the papillary muscles of the left ventricle, extending to the base of the heart, i.e., to a level higher than the site of the injection (Fig. 5).

*Specimen No. 65.*—Blue gelatine was injected into the anterior descending coronary artery at about its mid-point. The pressure on the gelatine masses in both the aorta and the branch was 180 mm. Hg. The result was a wedge-shaped area

of injection extending through the thickness of the anterior ventricular wall, but showing some indication of a laminar pattern in the intraventricular septum.

*Specimen No. 66.*—Blue gelatine was injected into the first large branch of the anterior descending coronary artery, and clear gelatine into the aorta. The pressure on both masses was 180 mm. Hg. The result was a wedge-shaped area of injection in the lateral wall of the left ventricle, extending from the site of injection to the apex and through the whole ventricular wall. There was no sign of a laminar pattern.

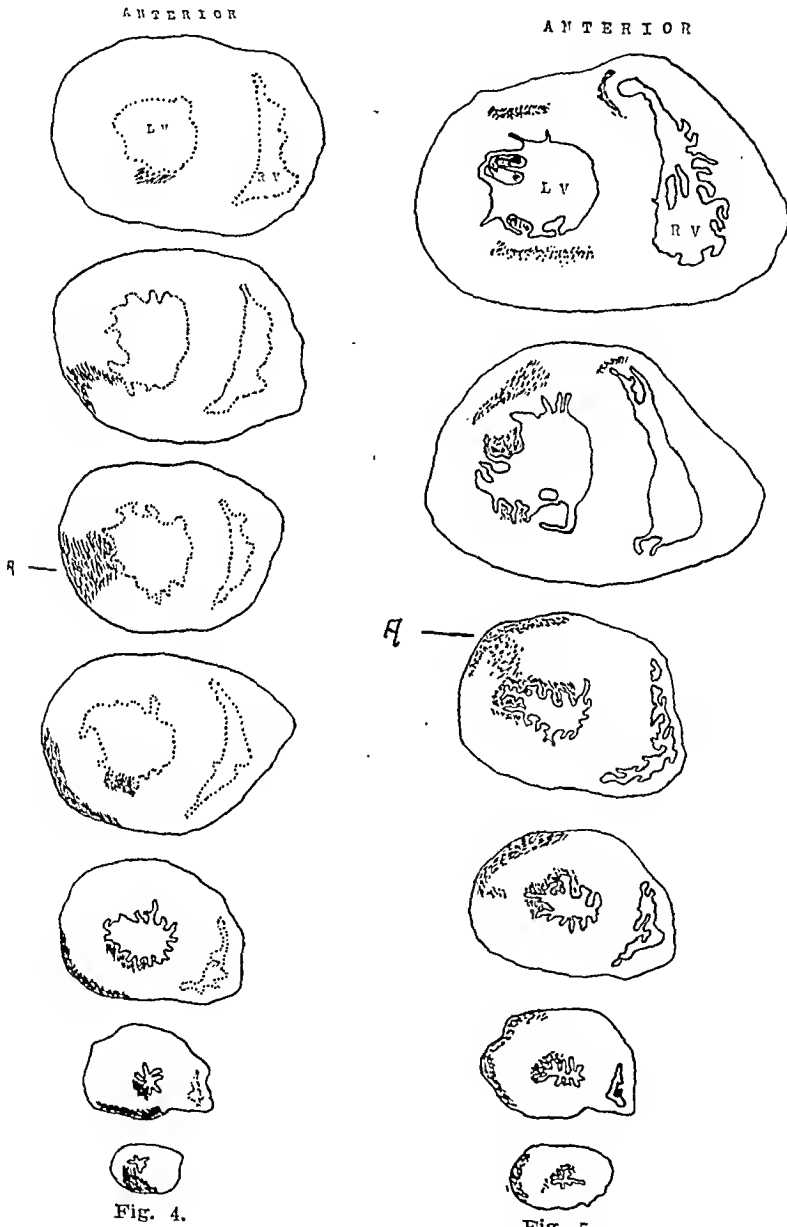


Fig. 4.

Fig. 5.

Fig. 4.—Drawing showing extent of injection in Specimen 70.

Fig. 5.—Drawing showing extent of injection in Specimen 71.

In all cases it was noticed that the extent of the blue injection masses increased after the hearts had been in hydrogen peroxide for some time.

Also, in the drawings the injected areas have been shown as if they had clear-cut boundaries. At their lateral extremities, however, it was usual to find a series of islands of injected tissue extending further than is indicated, but in the same general plane.

#### COMMENTS ON THE EXPERIMENTS

There are several observations to be made from these experiments. First, if the blue mass is injected into a branch of the coronary system under the same pressure as that previously ascertained by perfusion, the injected area of heart muscle is laminar and follows closely the anatomic relationships of the muscle concerned. The injection is not, however, completely confined to the one muscle, for at the level of injection a wedge-shaped area of muscle is supplied with gelatine. This closely parallels the distribution of petechiae in the superficial bulbospiral muscle in a case previously reported (Lowe<sup>9</sup>). In that instance there was a wedge-shaped area of hemorrhage near the base of the heart, as well as muscle distribution of hemorrhages.

The second observation is that, if the pressure on the gelatine in the branch is greatly in excess of that normally pertaining to that branch, the injected material spreads outside the limits of any one muscle and fills a wedge-shaped area which involves the whole thickness of the wall over a considerable longitudinal extent. The gelatine passes through anastomotic channels into a block of tissue without regard to its fine anatomic muscle arrangement.

Third, in the experiment on Specimen 70, it was shown that, by varying the pressure on the gelatine in the branch, the extent of the area injected could be altered quickly within wide limits. This means that in this case there was a free anastomosis between the portion of the coronary circulation supplied by the branch and the rest of the system, and that the normal balance depends simply on pressure relationships between the various branches of the coronary arteries. The fields normally supplied by various vessels represent a dynamic, not a static, equilibrium between those vessels. With a gross discrepancy of pressures (Specimens 65 and 66), the blue gelatine in the branch spreads over a very large field, whereas, with balanced pressures (Specimens 69, 70, and 71), the injection is confined to specific muscles.

It also appears that metabolic activities in the muscle had not ceased at the time of the injections, for the assumption that these changes were continuing is the only simple explanation for the increase in extent of the blue areas when the muscle slices were immersed in hydrogen peroxide. Apparently, the Berlin Blue dye acts as a hydrogen acceptor and is decolorized in the process. When the tissue is killed by fixation and the colorless dyestuff is exposed to an oxidizing agent, it regains the color. The bleaching process was not very powerful, for in the areas in which there were large quantities of blue dye there was no noticeable

rednction. It was only at the periphery, where the quantities of dye were small, that the change was seen.

The results obtained by injecting Specimen 69 show that in this heart the balances of the cirenlation were upset by the arterial changes which preceded the scar formation. This was revealed, first, by the marked decline of pressure between the aorta and the coronary branch (190 mm. to 50 mm.), which offers a sharp contrast with the normal decline of 120 mm. to 80 mm. in Specimen 70 and 220 mm. to 150 mm. in Specimen 71, in which arterial changes were not marked, and, second, by the fact that not only the muscle, but also the scar tissue was injected; the scar was in the deep bulbospiral muscle, which is not normally supplied by this artery.

Reviewing the injection experiments, we find that two distinct types of results are obtainable. First, if the injection pressure in the small artery is too high, a large area of tissue which is not confined to any one bundle, but extends through the whole thickness of the ventricular wall, is injected.

Second, if the pressures are correct, the injected area is laminar, with outlying islands of injected tissue which are mainly confined to one muscle bundle.

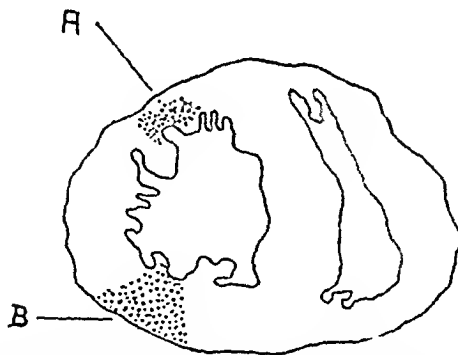


Fig. 6.—Drawing illustrating (A) massive scar, associated with thinning of the ventricular wall, and (B) massive infarct involving the whole thickness of the ventricular wall.

These injected areas bear a striking resemblance to the scars which are found in the ventricular muscle in arterial disease. These scars may be grouped into three distinct types, (1) that in which there has been large-scale destruction of the ventricular muscle, with subsequent replacement by fibrous tissue and frequently thinning of the ventricular wall (Fig. 6A); (2) that in which there is laminar scarring in the ventricular wall, sometimes associated with thinning of the wall (Fig. 7A); and (3) that in which the scar tissue is disseminated in islands throughout the ventricular wall (Fig. 7B). In addition to the scars, the large, wedge-shaped areas of infarction (Fig. 6B) which are found in some

cases of rupture of the ventricle must be included in the list of results of vascular obstruction.

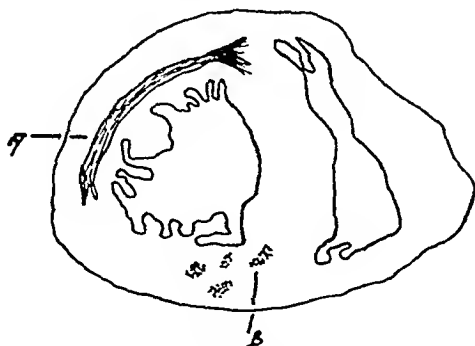


Fig. 7.—Drawing illustrating (A) a laminar scar in the ventricular wall and (B) disseminated islands of scar tissue.

The laminar injection areas, i.e., those limited to particular portions of individual muscles, correspond to the laminar scars described in detail by the author in previous papers.<sup>7, 8</sup> The wedge-shaped areas of injection resemble both the wedge-shaped scars (Fig. 6A) which are sometimes seen in the myocardium and the large areas of infarction (Fig. 6B) in ruptured ventricles and in cases of recent infarction which caused death. The outlying areas of injection are similar to the disseminated fibrosis that is so common in hearts which are the seat of gross atheromatous arterial changes.

#### DISCUSSION

Porter<sup>11</sup> wrote: "Everyone agrees that the coronary arteries anastomose. It is not the absence, but the character of the anastomosis, that is the basis of the present pathological teaching. The incontestable fact is that the anastomosis is too slight to permit a collateral circulation sufficient to keep a vascular area alive after the closure of the artery which supplies it."

The results of these experiments support Porter's statement that the vessels anastomose, but show that to say that a satisfactory collateral circulation cannot develop is correct only under very limited circumstances. Often a very efficient collateral circulation is formed. How much blood flows through an anastomotic vessel will naturally be determined by the pressure differences at the two ends of the channel. Normally, these differences are negligible, and, therefore, little blood will flow and the connections are overlooked (Fig. 8a', a'', a'''). If, however, changes occur in the pressure distribution in the system, blood will flow through anastomotic channels, and they then become very obvious (Fig. 9a'', a'''). If blood flows through the connecting vessels, those into which it flows become dependent upon a new parent vessel for their supply of blood. Thus, when we consider the fields of supply

of various vessels, it becomes apparent that the supply of a given area of tissue may change.

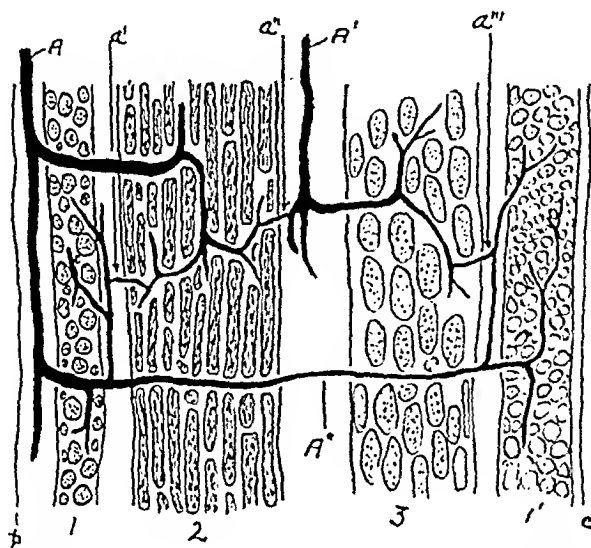


Fig. 8.—Diagram illustrating the normal arrangement of arteries among the muscle bundles of the ventricle.

*p*, pericardium; *c*, endocardium;

*A*, a subpericardial branch of the coronary arteries;

*A'*, an intermuscular branch of the coronary arteries (see Fig. 10);

*A''*, an arterial branch running through the thickness of the wall (see Fig. 11);

*a'*, *a''*, and *a'''*, nonfunctioning anastomotic channels;

*1*, the subpericardial layer of a superficial muscle;

*1'*, the subendocardial layer of the same superficial muscle;

*2* and *3*, layers representing two deep muscle bundles.

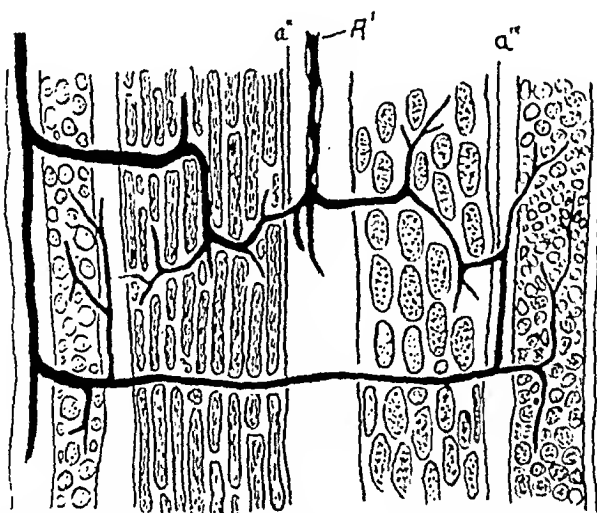


Fig. 9.—Diagram illustrating the redistribution of blood flow when one main vessel (*A'*) is partially occluded.

*a''* and *a'''*, anastomotic channels now functioning.

We must therefore envisage the blood supply fields as the result of a dynamic equilibrium (Fig. 12); and the boundaries between the fields will move, perhaps considerably, if the normal pressure distribution is



altered (Fig. 13). Naturally, if pressure disturbances are sudden and great, it will take time for complete readjustment, partly because of spasm of the vessels distal to the block, and also because the small anastomotic arterioles must develop into arteries. If sufficient time is available, compensation by redistribution of the blood supply may be perfect.

The evidence in favor of this conception is very strong. The areas supplied by the right and left coronary arteries in the normal (child's) heart, as defined by injections, have been shown to vary according to the pressure balance on the two gelatine masses.<sup>10</sup> If only one main vessel is injected, the mass spreads considerably into the field supplied by the other vessel, whereas, if both are injected together, the two fields are quite clear-cut. In Specimen 70 a similar result was obtained with a small branch of the coronary artery; it was shown that the area of injection could be controlled almost at will by varying the pressures on the injection masses.

In the experiments reported by the author in 1937, hearts were injected after tying a branch of one coronary artery, in the hope that one muscle bundle would remain uninjected. The results were very inconclusive; annular uninjected areas of varying extent were sometimes observed, but there were no separate uninjected muscle bundles. The reason for this is that a dynamic equilibrium exists between the vascular fields. Tying off one branch merely diverts the gelatine mass into other channels which more or less completely inject the field of the occluded vessel.

The effect of occlusive arterial disease is to alter the pressure distribution between the branches of the coronary system, and, consequently, to change the route of the blood through the tissue as a whole. With gradual occlusion, complete or partial, of a vessel, there is ample time for the establishment of new routes (Figs. 9 and 13), but sudden occlusion partially deprives an area of tissue of its normal blood supply until the new routes open up to full capacity (Fig. 14). It may happen that, in this interval, death of tissue takes place, sometimes with disastrous results to the function of the organ as a whole. There are many observations which support this view that the vascular fields are subject to alterations. Gross<sup>12</sup> observed arterial anastomoses in old hearts, in which they were functioning as new routes of supply; Schlesinger<sup>13</sup> demonstrated them clearly by injecting hearts which were the seat of occlusive arterial disease; and the author (1937) showed that they existed, but did not function, in the child. It is well known that one main coronary artery may be found to be occluded at post-mortem examination, and yet the heart muscle may show no evidence of gross damage. There have also been several instances in which the heart continued to function for long periods after all three main coronary branches were occluded. Specimen 69 showed definite evidence of this

readjustment of vascular fields, for the blue gelatine entered the scar tissue in the deep bulbospiral muscle from a vessel which normally does not supply that muscle. In this instance the readjustment of the circulation was not made quickly enough to save the whole of the muscle from death, but the injection showed that sufficient blood flow from new routes was available to keep alive the scar tissue and the few remaining muscle fibers in that region.



Fig. 10.

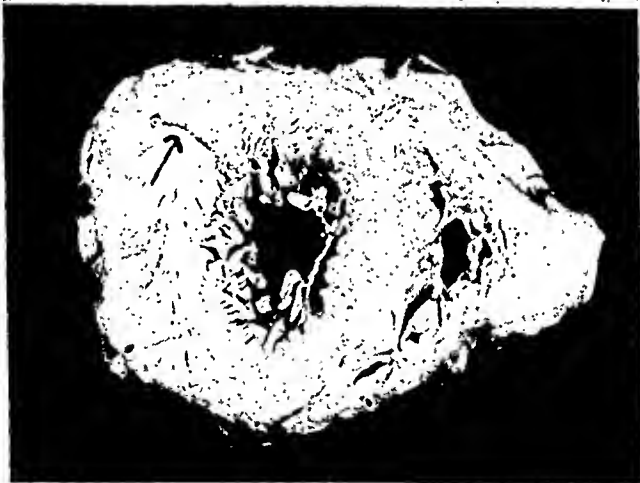


Fig. 11.

Fig. 10.—Photograph of an injected heart, showing arterial branch running between muscle planes.

Fig. 11.—Photograph of an injected specimen, showing arterial branch penetrating from the surface to the subendocardial layers.

Gradual occlusion of one or more vessels, therefore, merely brings about a redistribution of the blood supply. The effect of sudden occlusion is to deprive an area of tissue temporarily of the bulk of its supply. The extent of the area so deprived will of necessity be grossly different in a heart in which there have been gradual arterial occlusive changes and in one whose circulation is normal (Figs. 14 and 15). In the

former, the size of the area deprived of blood supply will depend on whether the occluded vessel took over a greater field in the redistribution, or was largely deprived of its field by the occlusion. If the occluded vessel had become a main channel to a large area, a large area

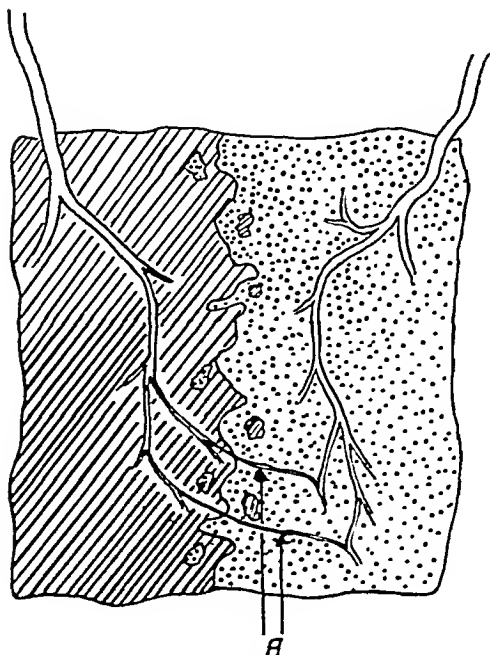


Fig. 12.

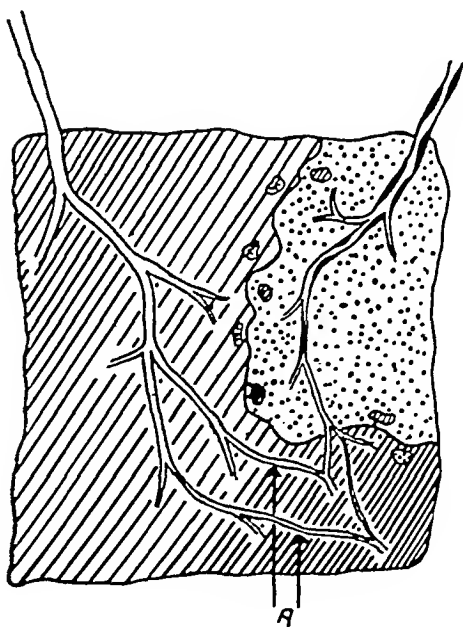


Fig. 13.

Fig. 12.—Drawing illustrating the normal fields of supply of two arteries. Non-functioning anastomotic vessels (A) shown. Drawing also illustrates the irregular and overlapping boundaries of these fields.

Fig. 13.—Drawing illustrating the change in fields of supply when one vessel is much more obstructed than the other. Anastomotic vessels now functioning (A).

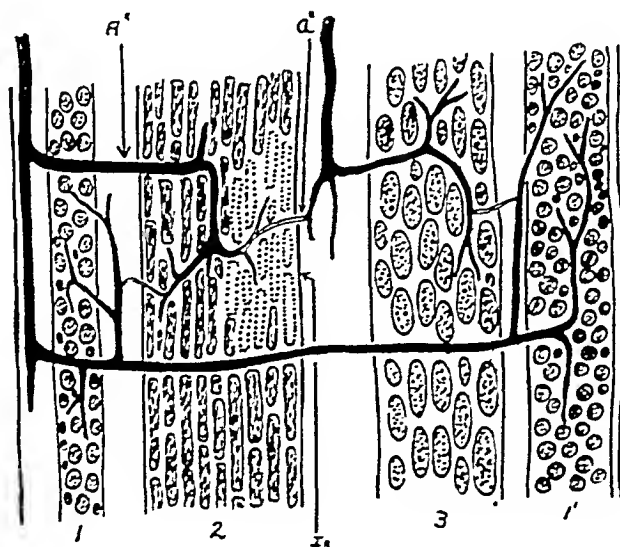


Fig. 14.—Diagram illustrating the effect of sudden obstruction of a small branch of the coronary artery  $A'$ . Because of spasm, the anastomotic channel  $a''$  is not functioning. The resultant infarct (In) is shown in dotted outline, and is confined to one muscle bundle (2).

will be rendered ischemic, whereas, if it were carrying very little blood, the area affected will be small. Sudden obstruction of a certain vessel

in a normal heart, e.g., by embolism, may produce an area of infarction (Fig. 14), but in a heart with occlusive arterial changes, occlusion of this vessel may produce almost no effect, or it may involve a vastly more extensive area than in the normal heart (Fig. 15). These areas vary from small, discrete islands to large, wedge-shaped infarcts which may involve the entire thickness of the ventricular wall, depending on which vessel is affected.

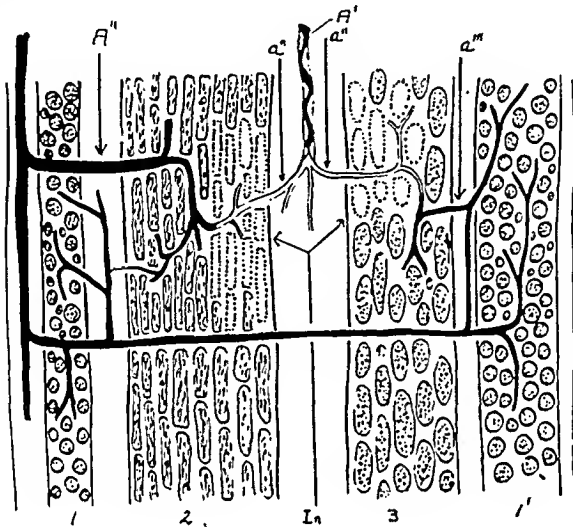


Fig. 15.—Diagram illustrating the effect of sudden obstruction of the same vessel as shown in Fig. 14, but in a system which is the seat of occlusive changes. The resultant infarct now involves two muscle bundles (2, 3). A', artery almost completely occluded by obstructive changes; a'', anastomotic vessels which were carrying blood from artery A'', but are now deprived of blood supply by obstruction of A'' branch. a''', anastomotic vessel carrying some blood, but an insufficient amount to prevent the formation of an infarct (1n).

Because there are distinct muscle layers and arteries both in planes between the muscle layers (Fig. 10) and passing directly through the muscle wall to the subendocardial layers (Fig. 11), the area of infarction may be confined to one muscle layer. It is also clear that, although obstruction of a vessel when the circulation is normal may produce an infarct limited to one muscle (Fig. 14), if there has been a readjustment of the circulation as a result of occlusion of arteries, obstruction of that same vessel may produce an infarct involving more than one muscle (Fig. 15). A similarity between laminar scars and laminar injections and between wedge-shaped injections and scars is therefore to be expected; the result will depend on the unpredictable vascular rearrangement.

There is, however, another possible and likely explanation for the multiple, discrete islands of fibrosis which are commonly seen in atheromatous hearts. If the occlusive changes are general throughout the larger vessels, there will be a reduction in the total quantity of blood available for distribution. In such circumstances, no rearrangement of paths will prevent the peripheral parts from receiving an inadequate

supply. These parts will therefore die and be replaced by islands of scar tissue (Fig. 16). The fact that there are islands of injected tissue at the periphery of the injected fields and that the dye is reduced by the metabolic activity in that region is evidence in support of this contention. It also suggests that, before death takes place, there will be a period of increased utilization of the oxygen available in the blood.

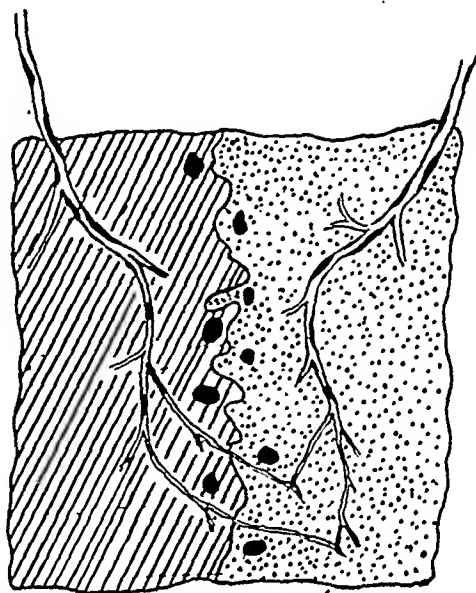


Fig. 16.—Drawing to illustrate the islands of dead tissue (black) at the periphery of the vascular fields when there is gradual, severe, and equal occlusion of both arteries.

The principle that there is a dynamic balance of blood flow between the branches of the coronary arteries therefore affords a simple explanation of the various types of scarring which occur in the myocardium. It also accounts for the discrepancies in the results obtained by various observers who have injected the coronary arteries with different substances.

#### APPLICATIONS

In as much as this conception of a dynamically balanced circulation is fundamental to the understanding of the pathologic changes in hearts which are the seat of occlusive arterial disease, it is not surprising that it also gives a clue to the meaning of the symptoms of this disease. Further, since it is a general principle, it should be of value in interpreting the results of arterial occlusion in any organ.

Considering first the heart, we find that clinical evidence indicates that there are varying types of symptom complexes. If the arterial changes result in gradual death of islands of muscle tissue, there will be a reduction in the amount of muscle available. The maximum effort of which the heart is capable is therefore reduced, and attempts to exceed this lowered maximum will be limited either by pain or dyspnea. An increasing extent of these lesions will lead to increasing severity of the

symptoms. Sudden vascular disturbances, such as thrombosis, will, if they cause infarction, produce a sudden lowering of cardiac reserve. The infarcts will vary in size from small areas to massive blocks of muscle, and the symptoms range all the way from those of a sudden, slight reduction of maximum output to severe attacks of pain and sudden death.

The manifestations of the occlusive arterial diseases of the leg are similar, namely, angina eruris, fatigability of the legs, and infarction of portions of the posterior tibial muscles as a result of vascular occlusion.

Consideration of the vascular lesions of the brain shows the same sequence. Pathologically, there are areas of degeneration and sclerosis which vary considerably in extent, and the large areas of infarction caused by cerebral thrombosis are well known. The corresponding symptoms vary from loss of memory, with the minor, diffuse lesions, to the syndromes caused by local lesions, such as paralysis agitans and the hemiplegia of sudden cerebral thrombosis.

In the kidneys, in cases of atherosclerosis, the lesions vary from small islands of scar tissue to massive infarcts.

Although this discussion has centered around the results of atherosclerotic vascular occlusion, the conclusions are equally applicable to syphilitic arteritis, thromboangiitis obliterans, or any other occlusive arterial process.





	TYPE OF INFARCT	RESULT
	Large mass of tissue involving whole thickness of ventricular wall	Sudden death Rupture when infarct softens
	Large mass of tissue not involving whole thickness of wall	Sudden death Rupture when infarct softens Aneurysm of ventricle
	Portion of one muscle	Aneurysm of ventricle Laminar scar (varying degree of myocardial inefficiency)
	Disseminated islands of tissue	Disseminated islands of scar (varying degrees of myocardial inefficiency)

Fig. 17.—Table showing the consequences of various types of cardiac infarction.

This study of myocardial scars leads to some conclusions concerning the events which follow the sudden obstruction of a coronary artery (Fig. 17). The production of an infarct involving the whole thickness of the ventricular wall will lead, if death does not ensue immediately, to rupture of the ventricular wall when softening takes place in the infarct. An infarct which does not involve the entire thickness of the ventricular wall will produce a weak spot in the wall when it softens

and will lead to rupture if the overlying muscle layers are not strong enough to resist the intraventricular pressure. This was well illustrated in the case reported recently by the author.<sup>9</sup> If rupture does not occur at this weak point, there will be gradual stretching of the scar, leading to aneurysm formation, which carries with it the liability to subsequent rupture and endocardial thrombosis. The infarction of a large portion of one of the deep muscles, giving rise to the laminar scars which are often seen in cases of aneurysm of the ventricle, may be taken as a particular example of this type of lesion.

The degree of myocardial impairment depends not only on the absolute amount of muscle destroyed, but also on its anatomic situation. Robb, Hiss, and Robb<sup>14</sup> showed that the superficial muscles were dynamically relatively less important than the deep muscles.

Unless we have a way to ascertain the type and extent of the infarction, and the muscles concerned therein, the outcome of coronary occlusion is unpredictable. It seems probable that electrocardiographic studies may provide the means of identifying types of infarction. For many years classical abnormalities in the electrocardiogram have been recognized as indicating anterior or posterior wall infarction (Bohning and Katz<sup>15</sup>). More recently, Robb and Robb<sup>16</sup> have attempted to identify the type of tracing associated with individual muscle lesions. Blood pressure measurements may be helpful in estimating the outcome, either by indicating that a deep muscle bundle is involved or that the pressure throughout the whole coronary system is lowered, which would mean that the blood supply to areas not primarily involved in the infarction was deficient.

If all of this information were available, it would be possible to say, with respect to any particular coronary occlusion, that aneurysm formation, rupture of the ventricle, or impairment of cardiac function was, or was not, likely. Until such information is obtainable, we cannot give an accurate prognosis. Even if it were we could never say that there would not be another occlusion at a subsequent date.

In recent years there have been many attempts to supply a new collateral circulation to the heart which is the seat of occlusive arterial disease, either by producing adhesions between the pericardial layers, or by attaching extracardiac tissues (skeletal muscle) to the ventricular wall. The object in both cases is to develop anastomoses between coronary and extracardiac arteries. Whether or not this objective will be achieved depends on the pressure relations in the vessels concerned, and King<sup>17</sup> has shown that the pressure distribution is not always favorable to the development of such a collateral circulation.

#### CONCLUSIONS

The evidence that there is a series of separate muscle bundles in the ventricular wall of the mammalian heart, and that they function in-

dependently, is now very strong. The proof no longer rests entirely upon anatomic dissections and preparations, but is supported by injection studies of the coronary circulation and by investigation of the distribution of pathologic processes in the ventricular walls.

Not only do the results of the injection experiments confirm the anatomic studies, but they also indicate that a balanced anastomotic coronary circulation is a normal phenomenon.

It is further obvious that this principle of a balanced anastomotic circulation is applicable to occlusive arterial disease in any organ.

That the efficiency of an anastomotic circulation which develops when an artery is occluded depends on the state of the collateral vessels is no new thesis. However, it is not generally recognized that there is a continuous dynamic balance between the flow in these various vessels. This conception of a dynamic balance in the circulation explains many phenomena which occur in the heart in occlusive arterial disease.

It is also clear that, at post-mortem examination of hearts which are the seat of obstructive arterial disease, it is necessary to examine all of the vessels, not merely those which normally supply the region where there is infarction or fibrosis, as the case may be.

Study of cardiac scarring also indicates clearly that the prognosis in cases of myocardial infarction varies considerably. The type of infarction which is likely to occur is entirely unpredictable because the character of the redistribution of the blood supply resulting from the arterial occlusion is unknown.

#### SUMMARY

1. A series of experiments in which colored and uncolored gelatine masses were injected into the coronary circulation is described.
2. In these experiments it was demonstrated that a gelatine mass could be injected into the vessels of a single ventricular muscle.
3. It was also shown that, in order to achieve laminar injection, a careful study of the pressures in the coronary system was necessary.
4. Several measurements of pressures at various points in the coronary circulation were recorded.
5. It is deduced that there is a dynamic balance between the fields of supply of branches of the coronary arteries.
6. This principle is used to explain the method of formation and the significance of the various types of myocardial scars in arterial occlusive disease.
7. The conclusions are applied in a general way to the pathologic study of occlusive arterial disease in all organs and are correlated with the clinical observations.
8. Some of the prognostic problems in cases of coronary occlusion are discussed.



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# A NEW PIEZOELECTRIC MANOMETER TO RECORD INTRACARDIAC PRESSURES AND FOR THE SIMULTANEOUS RECORDING OF INTRACARDIAC ELECTROGRAMS\*

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## I.

FOR the study of the effect of various agencies on the heart, it is frequently convenient to have simultaneous records of the electrical and mechanical manifestations of its activity. This can be accomplished in a number of ways; for instance, the classical form of the Frank-Wiggers manometer may be made to register pressure on part of the same film on which the electrocardiogram is being recorded. Although this method is capable of yielding accurate records, it is laborious and necessitates opening the chest of the animal and using artificial respiration. When two string galvanometers are at hand, a more convenient procedure is available. The pressure variations may be transformed into electrical changes that can be recorded with one of the instruments. In recent years the piezoelectric effect of Rochelle salt crystals has been utilized extensively for recording sounds and other vibrations, and it seemed probable that this method might also be employed to record pressure changes.

The apparatus (Fig. 1) which we devised for accomplishing this consists of a rugged housing (Fig. 1*B* 1), inside which a large slab of crystal (Fig. 1*A* *c*, and *B* 3) is secured at one end. The free end of the crystal is in contact with a diaphragm (Fig. 1*A* *b*, and *B* 5) which closes the end of a long, narrow cannula (Fig. 1*A* *a* and *B* 7), filled with saline solution. If certain limits are not exceeded, such a crystal can be made to produce charges which are accurately proportional to the pressure distorting it.

The problem of constructing an appropriate recording system involves two other considerations. First, the crystal must be connected to the string galvanometer in such a way that the static charges which develop under pressure are not dissipated too rapidly. This is accomplished by using a vacuum tube with a low grid current to couple the crystal to the galvanometer. Since the voltages developed by the crystal are relatively high, no amplification of the effect is needed, and a very simple circuit may be used.

The coupling of the crystal to the source of pressure is equally important. In this case the problem is to construct a system with a sufficiently high-frequency response. For this purpose a long cannula filled with salt solution is used. The end in contact with the crystal is closed with a very tightly drawn rubber diaphragm; the end which is inserted into the heart is left open. To prevent clotting, heparin is added to the salt solution with which the cannula is filled. The cannula is of small enough bore and sufficient length to be inserted into the heart by way of the jugular vein or the carotid artery. The cannula with its diaphragm is constructed

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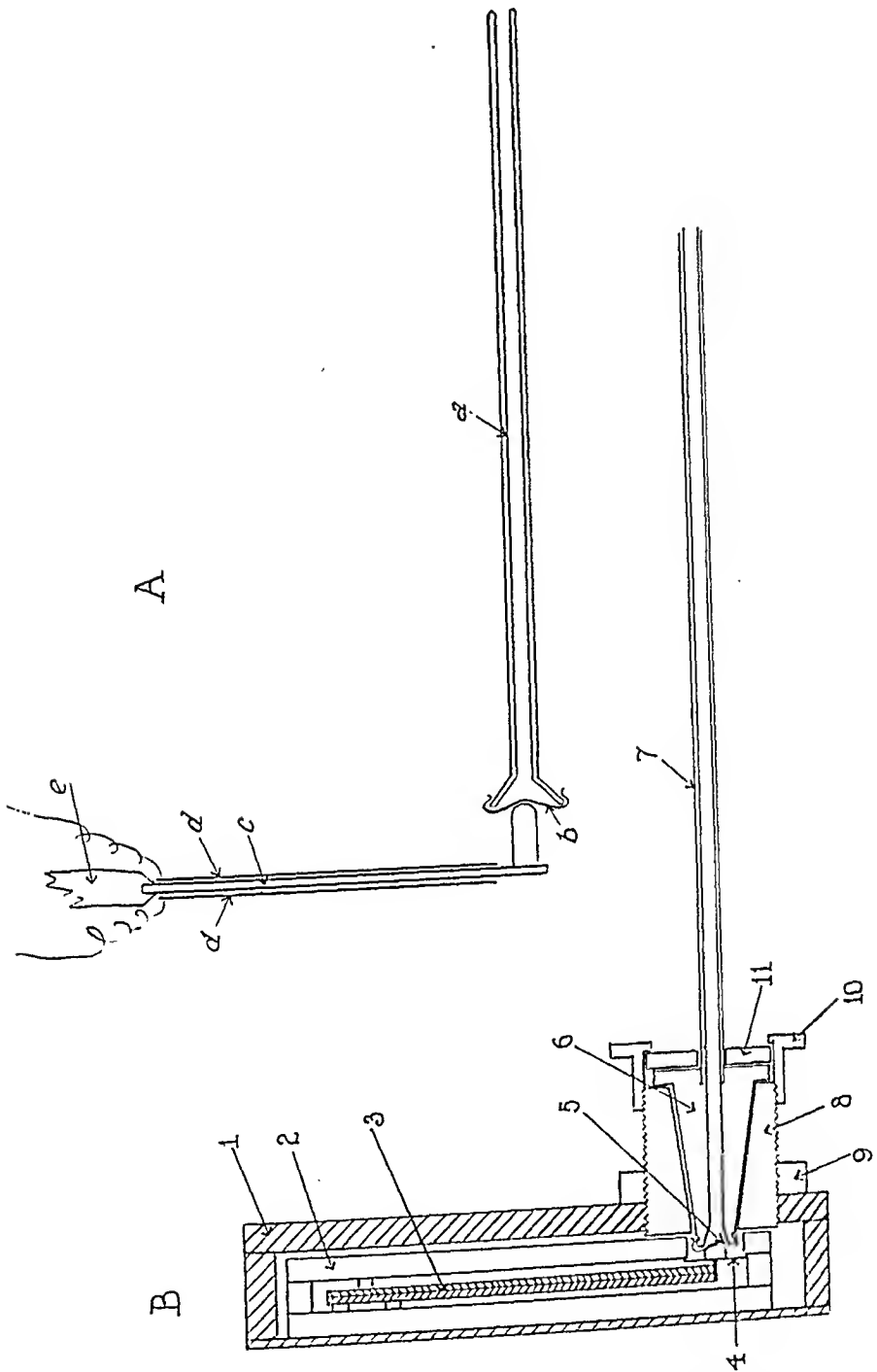


Fig. 1.—Piezoelectric manometer. *A*, Schematic drawing to illustrate the principle of operation. *a*, Cannula filled with salt solution; *b*, Distensible membrane which covers the end of the cannula and impinges upon a button connected to the free end of the cannula; *c*, slab of Rochelle salt crystal, held rigidly at one end by support *e*, and covered on both surfaces by plates of tin foil, *d*. When the open end of *a* is inserted into a chamber of the heart, the pressure changes which occur within it cause a distortion of the membrane, *b*, which, in turn, bends the slab of crystal, *c*. This deformation of the crystal causes its faces, which are covered by the tin foil, to assume opposite electric charges. If certain limits are not exceeded, these changes are proportional to the amount of deformation of the crystal, and, consequently, to the changes in pressure. *B*, Plan showing the actual construction of the manometer. 1, Rigid duraluminum outer case; 2, fiber inner case; 3, crystal; 4, diaphragm closing fiber case to protect crystal from moisture; 5, very tightly drawn rubber diaphragm, closing end of cannula; 6, the brass cone which forms the end of the cannula; 7, possible a very rigid connection between the cannula and the case of the crystal; 8,

as a single unit (Fig. 1B 5, 6, and 7) which is readily detachable from the crystal housing. It is filled with salt solution by means of a capillary pipette, and freed of air bubbles. Since the bore is so small that there is no danger of spilling the fluid, it is as easily manipulated as an empty cannula. The crystal housing, which is relatively large, need not be attached until the cannula is in the heart. A number of cannulae of different sizes are prepared at the beginning of the experiment, so that the appropriate size may be selected after the vessels are exposed.

Hamilton, Brewer, and Brotman<sup>1</sup> have discussed at length the frequencies attainable through narrow cannulae, and they probably adequately demonstrated their contention, but their work has not escaped criticism. It will not be redundant, therefore, to discuss from a different point of view the factors upon which the frequency responses of cannulae depend.

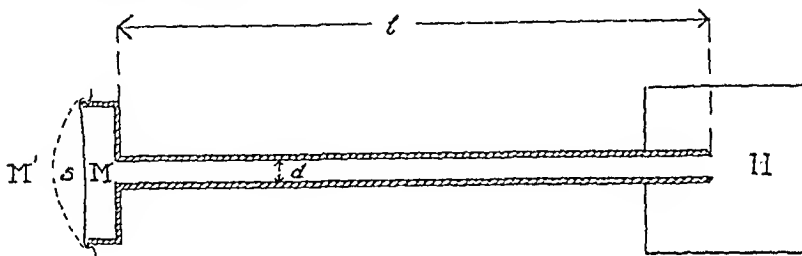


Fig. 2.

The cannula of length  $l$  (Fig. 2) is closed at one end by a distensible membrane ( $M$ ), and connected to a chamber ( $II$ ) in which the pressure varies. If the pressure in  $II$  is increased from  $P_1$  to  $P_2$ , the membrane will assume the form  $M'$ , and, consequently, an amount of fluid designated by  $s$  must pass through the tube. The speed with which this transfer can take place is the limiting factor in the frequency response of the cannula.

The principal forces which tend to retard the flow of fluid through the tube are inertia and friction. When small cannulae are used, the inertia of the fluid can be neglected, because it decreases with the bore. According to King's formula, the

retarding effect of friction is  $h_f = K \frac{l}{d^{1.25}} V^{**}$ .  $K$  is a constant which depends

upon the roughness of the tube;  $l$  and  $d$  are the length and diameter of the tube, and  $V$  is the mean velocity in centimeters per second. If this formula is expressed

in terms of  $s$ , the amount of fluid passing through it in time  $t$  (the time taken for the pressure to change from  $P_1$  to  $P_2$ ), it becomes  $h_f = 4K \frac{ls^2}{td^{5.25}}$ .

From the last equation it is apparent that an increase in length of the cannula ( $l$ ) increases the resisting force, but that a decrease in diameter ( $d$ ) increases it much more because this factor appears as the fifth power. Both of these effects can be counteracted, however, by a sufficiently great decrease in  $s$  (the distensibility of the membrane), which appears as the second power. Although it is clear from the equation what factors are involved, the precise extent to which a decrease in diameter can be compensated for by a decrease in the distensibility of the diaphragm cannot

the cannula is made of silver and insulated with baked-on lacquer, save for the tip; 8, the receptacle for the conical end of the cannula is threaded, so that the contact between the diaphragm closing the end of the cannula and the button connected to the free end of the crystal can be adjusted; 9, a lock nut to hold the receptacle rigidly once the correct position is found; 10, a threaded collar with an opening large enough so that it can be slipped over the conical end of the cannula after it has been inserted into the animal's heart; 11, A slotted disk which can be slipped around the cannula after it is in place to engage the threaded collar.

\* $n$  is usually 2, but may vary from 1.75 to 2.08.

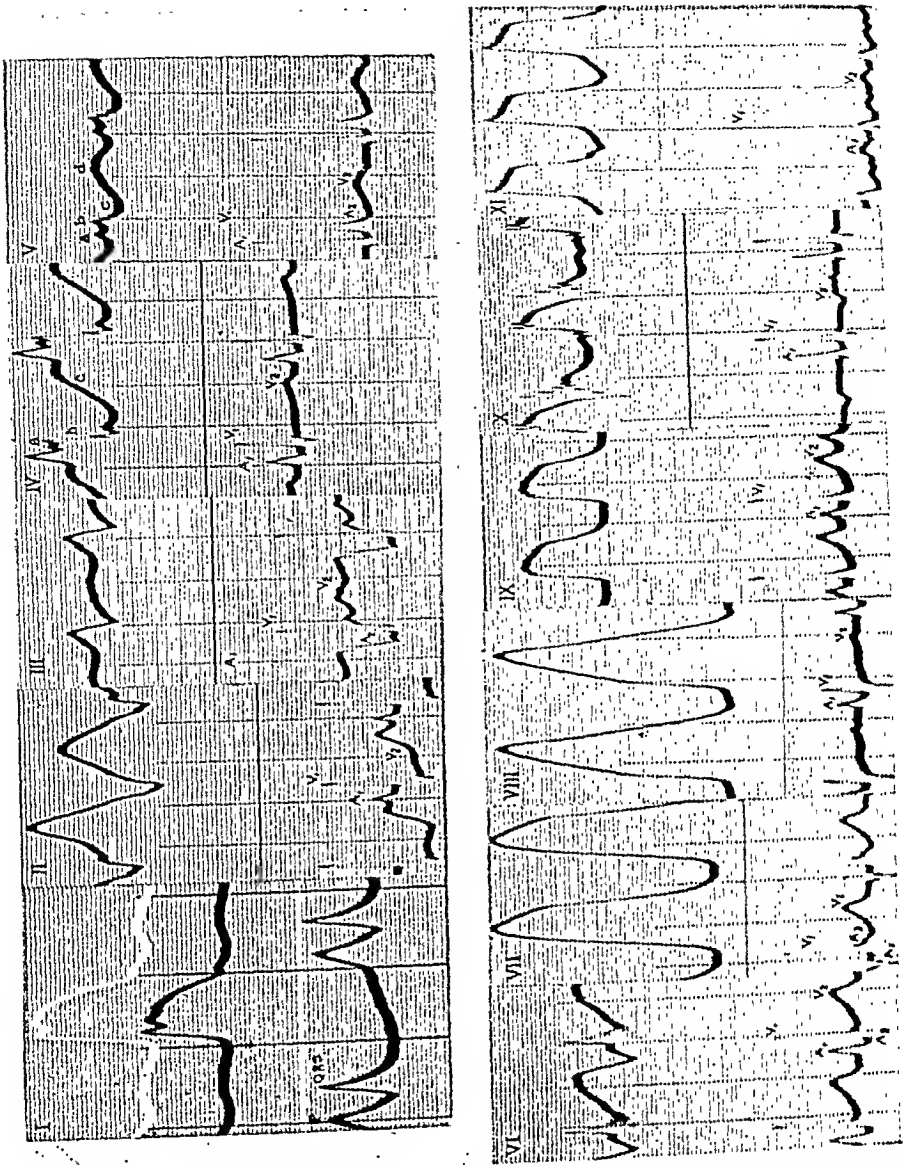


Fig. 3.—I, A comparison of curves obtained with piezoelectric and Frank Wiggers manometers. Top (white) curve, femoral pulse of a dog as recorded by the piezoelectric manometer; middle (black) curve, femoral pulse recorded by the Frank Wiggers manometer. The bottom curve is a simultaneously recorded electrocardiogram. II, Curves which exhibit the effect of inserting the cannula too far into the right ventricle of a cat, so that its tip came in contact with the wall. The pressure curve is deformed (cf. VII, VIII, and IX), and the ventricular electrogram tends to be of a monophasic type (the take-off of the T wave is below the isoelectric line). III, Curves which exhibit the effect of inserting the cannula too far into the right auricle of a cat, so that its tip came in contact with the auricular wall. The pressure curve is deformed (cf. IV and V), and the auricular electrogram tends to be of the monophasic type (A<sub>2</sub>). IV, Typical records from the right auricle of a cat obtained with an insulated cannula. The pressure curve (upper) shows an initial spike, *a*, caused by contraction of the auricle, followed, after a brief interval, by a sharp fall, *b*, and a subsequent gradual rise, *c*, which are caused by ventricular activity. The electrogram (lower curve) resembles an electrocardiogram. Auricular activity is registered by an upward spike (A<sub>1</sub>), followed by the two components of the ventricular complex, namely, V<sub>1</sub> (= QRS) and V<sub>2</sub> (= T). V, Records from the right auricle of a cat obtained with a cannula which was insulated, save for the tip. The pressure curve resembles IV, except that there is an additional positive phase, *d*, caused by auricular filling. In the electrogram (lower curve) the auricular response (A<sub>1</sub>) is diphasic and of much greater voltage than IV. It resembles the intrinsic responses which are obtained when an electrode is placed in direct contact with the exterior of the auricle. The regression process of the auricle (A<sub>2</sub>) is superimposed upon V<sub>1</sub>, which is the initial ventricular response. VI, When curves are recorded with an uninsulated cannula in close contact with the tricuspid valve of a cat, the first heart sound appears in the pressure curve. VII, Curves recorded with an insulated cannula in the right ventricle of a cat: A<sub>1</sub>, the auricular accession process, is downward, as is the intrinsic deflection from the

be predicted from it, but must be ascertained experimentally. The experiments of Hamilton, et al.,<sup>1</sup> have established the fact that cannulae much smaller than it has been necessary to use to enter the hearts of dogs and cats by way of the vessels in the neck can be employed without distorting the curves when the distensible diaphragm is a thin silver plate. The displacement ( $s$ ) of such a diaphragm is very small. Since even less movement of the diaphragm is required to operate the crystal than Hamilton requires for his optical method of recording, his experiments are applicable to the cannulae which are used with the piezoelectric recorder.

A convenient record of electrical activity to pair with the pressure curve is one which emphasizes the effect of the chamber that is being explored. This is particularly desirable in the case of the auricle, for, in ordinary electrocardiograms, the electrical effects of its activity are so small that no detailed analysis of them is possible. Since Wilson and his collaborators<sup>2, 3</sup> have shown that, when one electrode is very close to the heart, it is affected predominantly by the muscle closest to it, this result is easily accomplished by using the tip of the cannula as the exploring electrode. To this end, the cannula is made of silver and insulated, save for the tip, with baked-on enamel. The exposed tip is rendered nonpolarizable by giving it a coat of silver chloride. A silver plate, inserted beneath the skin of the animal's hind leg, serves as the indifferent electrode. An added advantage of using the tip of the cannula as the exploring electrode is that any impingement of the heart wall that might occlude or partially occlude its orifice is at once betrayed by the appearance of a monophasic response in the electrical record (Fig. 3II and III).

The complete assemblies, including cannulae and crystals, have inherent frequencies in excess of 100 per second, as indicated by the usual tests, but since the ability of this instrument to record the slow components of the curves must also be checked, a direct comparison was made with the classical form of the Frank-Wiggers manometer by inserting the cannula of the crystal recorder into the femoral artery of a dog, and that of a Frank-Wiggers manometer into a branch close enough to the main stem so that the tip protruded into it. In this way the mouths of the two cannulae were brought very close together. Practically identical curves were obtained from the two instruments (Fig. 3F). The cannula used on the crystal manometer in this instance was the same length, but smaller in diameter, than those used to enter the heart.

## II.

As the cannula is passed down the jugular vein of an animal, the pressure curves gradually increase in size until a typical intra-auricular pressure curve is obtained (Fig. 3IV and V). These curves are similar in contour to those of previous observers.<sup>4</sup> They nearly always show some rapid vibrations at the time of the occurrence of the heart sounds, particularly the first. When the cannula is pushed into the immediate vicinity of the tricuspid valve, these vibrations become marked (Fig. 3VI). When the cannula passes through the valve into the ventricle, the character of the curve changes abruptly into that of a typical intra-

exterior of the heart at the auriculoventricular junction. *A<sub>2</sub>*, The auricular regression process, is upward and continued with *V<sub>1</sub>*, which is diphasic; the second component is large and downward. *VIII*, Curves obtained with an uninsulated cannula in the right ventricle of a cat. *V<sub>1</sub>* is diphasic. *IX*, Curves from the right ventricle of a cat. *V<sub>1</sub>* is representative of the more usual monophasic type. *X*, Curves obtained with an insulated cannula in the aorta of a dog, near the aortic valve. The vibrations of the second heart sound can be seen in the pressure curve. *A<sub>1</sub>* resembles intrinsic deflections from the region of the sinus node. *XI*, Curves obtained when an insulated cannula is passed into the left ventricle of a dog. *V<sub>1</sub>* is monophasic.

ventricular pressure curve which usually shows no trace of the vibrations of the first heart sound (Fig. 3VII, VIII, and IX).

When the cannula is passed down the carotid artery, the carotid pulse which is recorded usually shows some trace of the second heart sound. When the cannula is close to the aortic valve, these vibrations are of considerable amplitude (Fig. 3X). After the ventricle is entered, the character of the curve abruptly changes to the intraventricular type (Fig. 3XI).

In the electrogram obtained from the interior of the right auricle the auricular complex is large, and both parts of it can be made out, i.e., the rapid accession process ( $A_1$ , Fig. 3V) and the regression or T deflection ( $A_2$ , Fig. 3V). The latter is usually combined with the ventricular part of the electrogram, but in many instances it can be seen quite clearly.  $A_1$  is usually diphasic, and the first phase is downward. When the cannula is near the junction of the great veins with the auricle, this downward phase is small (Fig. 3V); near the auriculo-ventricular junction it is larger; and in the upper part of the ventricle (Fig. 3VII) it (the downward phase) alone remains. The auricular regression deflection, as a rule, consists of a small, rounded, downward or upward deflection ( $A_2$ , Fig. 3V and VII) between  $V_1$  (QRS) and  $V_2$  (T). In some of the earlier experiments no insulating lacquer was used on the outside of the cannula; under these circumstances  $A_1$  consisted of a single upward phase (Fig. 3IV) which did not change in shape when the cannula was pushed into the ventricle (Fig. 3VIII).

### III.

Usually, electrograms from the interior of the two ventricles are similar; they consist of a single upward (negative) deflection ( $V_1$ ) of large amplitude, followed by an upward, downward, or nearly isoelectric T wave ( $V_2$ ) (Fig. 3IX and XI). Occasionally, from the right ventricle, curves are obtained in which the initial component is diphasic; the initial ( $V_1$ ) upward deflection is followed by a downward (positive) deflection (Fig. 3VII and VIII). The ventricular complexes obtained when the cannula is still in the auricular cavity resemble those from the ventricle, except that they are not so large.

If the crystal in the manometer is deflected by subjecting the cannula suddenly to a change of pressure, the crystal faces become charged, but these charges will gradually leak away, even when the pressure is maintained constant. Since the time required for these charges to dissipate is ten seconds or more, the rapidly changing pressures which accompany cardiac contraction are recorded accurately, but constant pressures are not recorded at all. Consequently, only pulse pressures can be measured with this instrument. For many purposes, however, this is sufficient, particularly if information is desired about the force of cardiac contraction rather than changes in the peripheral resistance. Since the crystal, when deflected, behaves like a condenser discharging through a high resistance, the lower the voltage, the less the rate of discharge, so that.

if a relatively small voltage is produced by deflecting the crystal only slightly, the accuracy of the record is increased. Since only a few millivolts are required to give records of good amplitude, one may use very stiff diaphragms which not only improve the performance of the crystal, but increase the frequency response of the cannulae.

The pressure curves obtained from the three chambers of the heart which can be explored with this type of manometer are similar to curves obtained by other appropriate means.<sup>4</sup> The value of the new instrument depends on its convenience and on the fact that the animals can be left intact and their circulation not interfered with. It has the advantage over the method of Hamilton, et al.,<sup>1</sup> which may also be used without opening the animal's thorax if a needle is thrust through the chest wall into the heart, that there is less uncertainty as to the position of the cannula, and that the animal need not be near the recording camera. The animal can be studied in an adequate light without interfering with photographic recording.

Only one type of pressure curve requires special comment, namely, that obtained in the immediate vicinity of the heart valves. These records may show sound-like vibrations which are coincident with valve closure (Fig. 3VI and X). These vibrations may be artifacts caused by impingement of the valves on the end of the cannula, or may be produced by closure of the valves (the valvular component of the heart sounds). Against their being artifacts is the fact that plucking (setting into vibration) the end of the cannula produced only very small vibrations in the record. It was, of course, necessary to construct the manometer so that sidewise tugging on the cannula would not distort the records with artifacts caused by motion of the heart. Obviously, after the cannula has entered the ventricle, the valve leaflets must still be impinging upon the cannula, but, nevertheless, the vibrations disappear. Brewer, Hamilton, and Brotman<sup>5</sup> have shown that very abrupt changes in pressure may set the recording system into vibration if its inherent frequency is not sufficiently high, but pressure changes quite as abrupt as those which occur at these points in the curves are not always associated with sound-like oscillations, notably the sudden rise in pressure during the isometric contraction phase. The conception of Brewer, Hamilton, and Brotman that practically all cardiovascular sounds are in reality caused by sudden changes in pressure which set the recording system or the eardrum into vibration is probably too sweeping. There can be no doubt that the heart sounds, for instance, are really sounds (repeated oscillations) at the anterior chest wall, for microphones capable of responding to frequencies as high as 30,000 cycles per second always record them as sounds consisting of many oscillations. Sudden changes of pressure occur when the myocardium contracts or the valves close, and these changes, when they are applied to adjacent inert tissues, will inevitably cause them to vibrate. Therefore, the first and second



heart sounds cannot be considered as instrumental vibrations unless all of the tissue between the source of shock and the surface of the body is regarded as part of the recording instrument. Although the vibrations which are recorded from the immediate vicinity of the valves by means of this new manometer may be some sort of artifact, they may also reflect the vibrations, caused by closure of the valves, which are transmitted to the surrounding tissues as the valvular components of the heart sounds.

Electrograms from the interior of the heart have not been recorded frequently,<sup>6</sup> for, although they have considerable theoretical interest, they have been of little practical value because of the difficulty in obtaining them. Since they are easily obtained with this new device and may prove to be useful records of the heart's electrical activity, they should be discussed briefly.

Wilson, Macleod, and Barker<sup>3</sup> showed that electrograms taken with an exploring electrode in contact with the auricle show intrinsic deflections which are similar to those obtained from the ventricle, but they can be obtained only when the electrode is very close to the auricular surface, whereas intrinsic-like deflections can be obtained from the ventricle even through the chest wall.<sup>7</sup> The electrograms from inside the auricle which were recorded in the course of this study resemble those taken from comparable positions on the outside. This similarity is to be expected, because an impulse which spreads radially bears the same relative position to any electrode which it passes, whether the latter be inside or outside the auricle, and because the conductivity of the blood is not very different from that of the tissues which surround the heart.

These electrograms from within the auricle are larger than those which Brown<sup>8</sup> obtained with an electrode in the esophagus, but not quite as large as those obtained by the usual methods from the exterior surface. The auricular complexes of the curves obtained from the aorta near the aortic valve (Fig. 3X) resemble Brown's curves closely.

Although it is impossible to know accurately to what part of the auricular muscle the tip of the cannula is nearest, the change in the shape of the curves as the cannula is pushed through the auricle is what would be expected from the work of Wilson, Macleod, and Barker.<sup>3</sup> An early intrinsic deflection, with a small, preceding, downward deflection, is obtained when the cannula first enters the auricle by way of the superior vena cava and is near the sinus node (Fig. 3V, A<sub>1</sub>). In the auriculoventricular region the intrinsic deflection is late, and, in the upper part of the ventricle, it disappears, and the complex consists of a downward deflection only (Fig. 3VII, A<sub>1</sub>). Curves of an intermediary type (the upward and downward phases of which are more or less equal) are not usually obtained because the cannula passes through the auricle from the orifices of the great veins to the auriculoventricular region without coming in close contact with the mid-portion of the auricular wall.

Because it is too small, the P wave of the electrocardiogram has been of comparatively little use in studying the condition of the auricular myocardium. It has, for instance, been known for a long time that the P wave is only that part of the auricular activity which corresponds to the QRS group of the ventricular complex; the part corresponding to the T wave is usually too small to be seen.\* In electrograms taken directly from the surface of the auricle, and in Brown's curves from suitable positions in the esophagus, the T portion of auricular activity can be readily identified. In normal curves from the interior of the auricle, this TA deflection (Hering), or auricular regression deflection (Macleod<sup>11</sup>), usually falls in the QRS complex, and, consequently, is not easily recognized (Fig. 3V and VII, A<sub>2</sub>). It may, however, as Brown has pointed out, deform the S-T segment; it may also account for the failure of the curve to return to the isoelectric line during the P-R interval. As will be shown in a subsequent paper,<sup>9</sup> alterations in this process are often very easily seen, although, in its normal form, it is inconspicuous. That the auricular regression deflection is a delicate index of the effect of drugs and other agencies on the auricular myocardium has been shown by Cohn and Macleod,<sup>10</sup> and Macleod.<sup>11</sup> It is, therefore, particularly desirable to be able to study this deflection in mammals.

Wilson, Johnston, and Hill,<sup>12</sup> in their study of myocardial infarction, described electrograms which were taken from the interior of the ventricles. The QRS of their curves consists of a single, tall, upward (negative) deflection. This is the type of curve which is to be expected if the impulse is conducted rapidly over the endocardial surface by means of the Purkinje network, and subsequently spreads outward through the ventricular wall at a slower rate. The curves which were obtained from the left ventricle in the course of the present study were always of this form. Those from the right ventricle were usually of the same type, but occasionally, both in dogs and cats, curves were encountered which showed a prominent downward (positive) deflection after the upstroke. The explanation of this deflection is not at once apparent; its presence might seem to be inconsistent with the view of Wilson, Johnston, and Hill, but, by utilizing the same principles upon which their concept is based, and taking into consideration certain anatomic facts, one can account for it.

Wilson, Macleod, and Barker<sup>13</sup> have explained how the active process can be likened to an expanding shell, so polarized that its outward surface is positive and its inner surface is negative, spreading outward through the ventricular muscle. An electrode in the left ventricle (L, Fig. 4) is exposed only to the negative surface of this shell throughout the period of excitation. Although it is true that the septal portion of the right ventricular shell has its positive surface towards electrode L,

\*Brown's paper<sup>9</sup> contains a full account of the history of this deflection.

the effect of this is always neutralized by the septal part of the left ventricular shell.

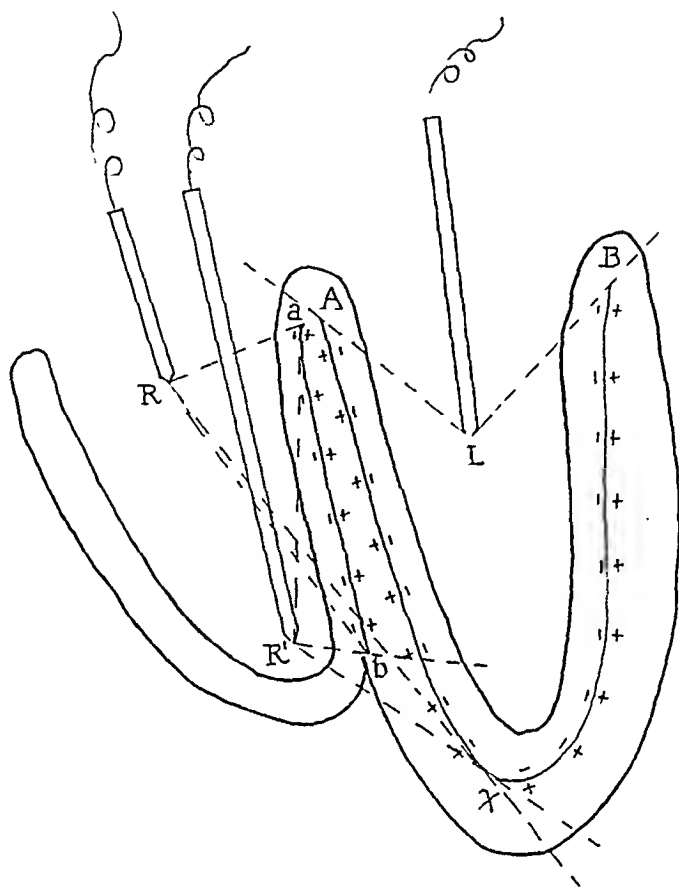


Fig. 4.

Electrode *R*, in the right ventricle, like *L* in the left, will be negative until its expanding shell reaches the outer surface of its lateral wall and disappears. Now only the septal portion remains. If the electrode is so placed (*R*) that this portion masks the positive surface of the left ventricular shell, it will remain negative or become zero, but, if the electrode is at *R'*, this septal portion of the right ventricular shell is insufficient to do this, and the electrode will become positive during the later part of the period of excitation.

#### SUMMARY

1. A manometer which simultaneously records intracardiac pressure curves and intracardiac electrograms is described.
2. Criteria are presented for estimating the accuracy of the pressure curves obtained with this apparatus.
3. Electrograms obtained with the noninsulated tip of the manometer as it is pushed progressively farther through the right auricle, the A-V valve, and into the ventricle demonstrate changes in the action currents corresponding to these levels.

4. The form of the electrogram obtained from within the ventricle is likewise discussed.

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# THE EFFECT OF ACETYLCHOLINE ON THE MAMMALIAN HEART

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## I.

COHN and Macleod<sup>1</sup> have recently published a study of the effect of mechohyl and acetylcholine on the frog's heart. This study indicated the general mode of action of the drug, but, because choline derivatives are being used to a considerable extent clinically, particularly for the relief of attacks of paroxysmal tachycardia, and because the vagus mechanism of mammals is somewhat different from that of frogs, it seemed desirable to extend these studies to the mammalian heart. The effect of the drugs on the mechanical response of the heart could, furthermore, be more easily studied in the mammal because of its greater size.

The experiments were carried out on cats and dogs which were anesthetized with nembutal. The vagi were exposed and cut. Stimulating electrodes were attached to their peripheral ends. The cannula of the piezoelectric manometer, insulated except at its tip, which was described in a previous paper<sup>2</sup> was inserted into the heart by way of a jugular vein or carotid artery. The intracardiac pressure pulse was recorded, together with an electrogram derived from the tip of the cannula (exploring electrode) and a silver plate inserted under the skin of the left hind leg (indifferent electrode). Simultaneous records of the electrical and mechanical activity of the heart were obtained by this means without opening the animal's thorax. Records were obtained from the right auricle and the right ventricle by pushing the cannula through a jugular vein, and from the left ventricle by inserting it into a carotid artery. The drugs were administered intravenously. A dose of 1 to 2 mg. of acetylcholine (or about one-tenth that amount of mechohyl) was used for the average cat; dogs required 5 to 7 mg. of acetylcholine to obtain an equivalent effect.

## II.

### AURICLES

The earliest effect of stimulation of either vagus is slowing of the auricular rate. Accompanying, or immediately following, this, there is diminution in the force of auricular contraction (negative inotropic effect, Fig. 1 *II*, and *III*). At about the same time there are alterations in the auricular regression deflection (Fig. 1 *III*, *A<sub>2</sub>*). After strong stimulation, marked shortening of this process occurs. The first observable effect, however, is a deformity of the segment which immediately follows the accession deflection (in the P-R region). It is difficult to be certain whether these changes precede, accompany, or follow the reduction in the force of contraction (the relationships differ in different experiments), but, in any case, they are nearly coincident with it. During the height of vagus action the amplitude of the whole of the auricular electrogram is reduced (Fig. 1 *III*). Prolonged stimulation occasionally initiates a brief paroxysm of auricular fibrillation.

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Acetylcholine produces similar results (Fig. 1 *IV*, *V* and *VI*), except that the changes are of greater magnitude; that part of the intra-auricular pressure curve which results from auricular contraction may entirely disappear (Fig. 2 *I*). The auricular regression deflection is

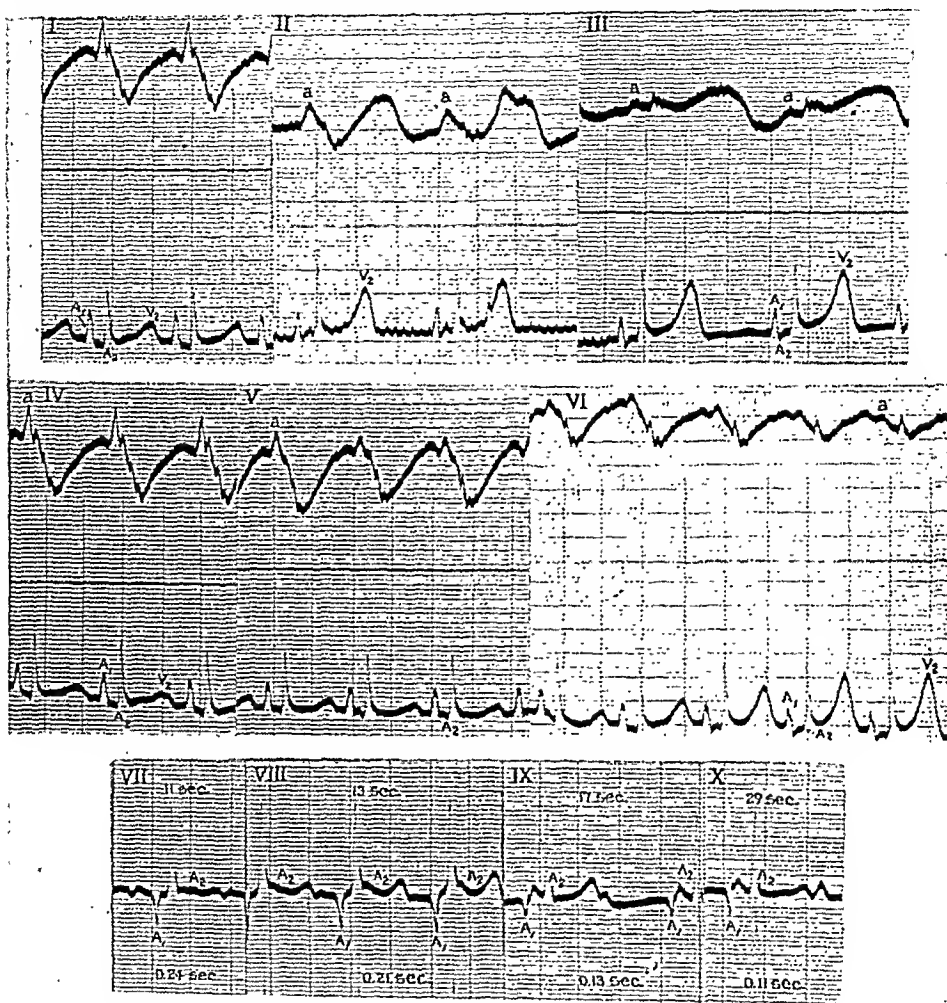


Fig. 1.—The effect of vagus stimulation and acetylcholine on the intra-auricular pressure curve during auricular contraction. *a* is the component of the auricular pressure curve caused by auricular contraction. *A*<sub>1</sub> represents the accession process in the auricular electrogram (P wave). *A*<sub>2</sub> is the regression process in the auricular electrogram (Ta wave). *V*<sub>2</sub> is the regression process in the ventricular electrogram (T wave). *I*, *II*, and *III* were taken before, during, and just after left vagus stimulation. *II* and *III* show a negative inotropic effect in the auricles. They also exhibit small ripples caused by escape of the stimulating current. *IV* was taken before injection of acetylcholine; *V*, seven seconds after the injection of 2 mg. acetylcholine; and *VI*, about ten seconds after injection. *VII*, *VIII*, *IX*, and *X* are electrograms obtained with the electrode inserted just inside the ventricle of a cat. They show shortening of electrical systole and a decrease in voltage of the auricular complex. The figures above each curve give the time after an injection of 2 mg. of acetylcholine; those below, the duration of electrical systole (from the beginning of the accession process to the end of the regression process).

greatly shortened (Fig. 1 *VII-X*). (Since heart block nearly always occurs at this stage, the changes in this process are undistorted by any ventricular effects.) The reduction in size of the entire auricular electrogram is marked (Fig. 2 *I*). Auricular extrasystoles usually occur

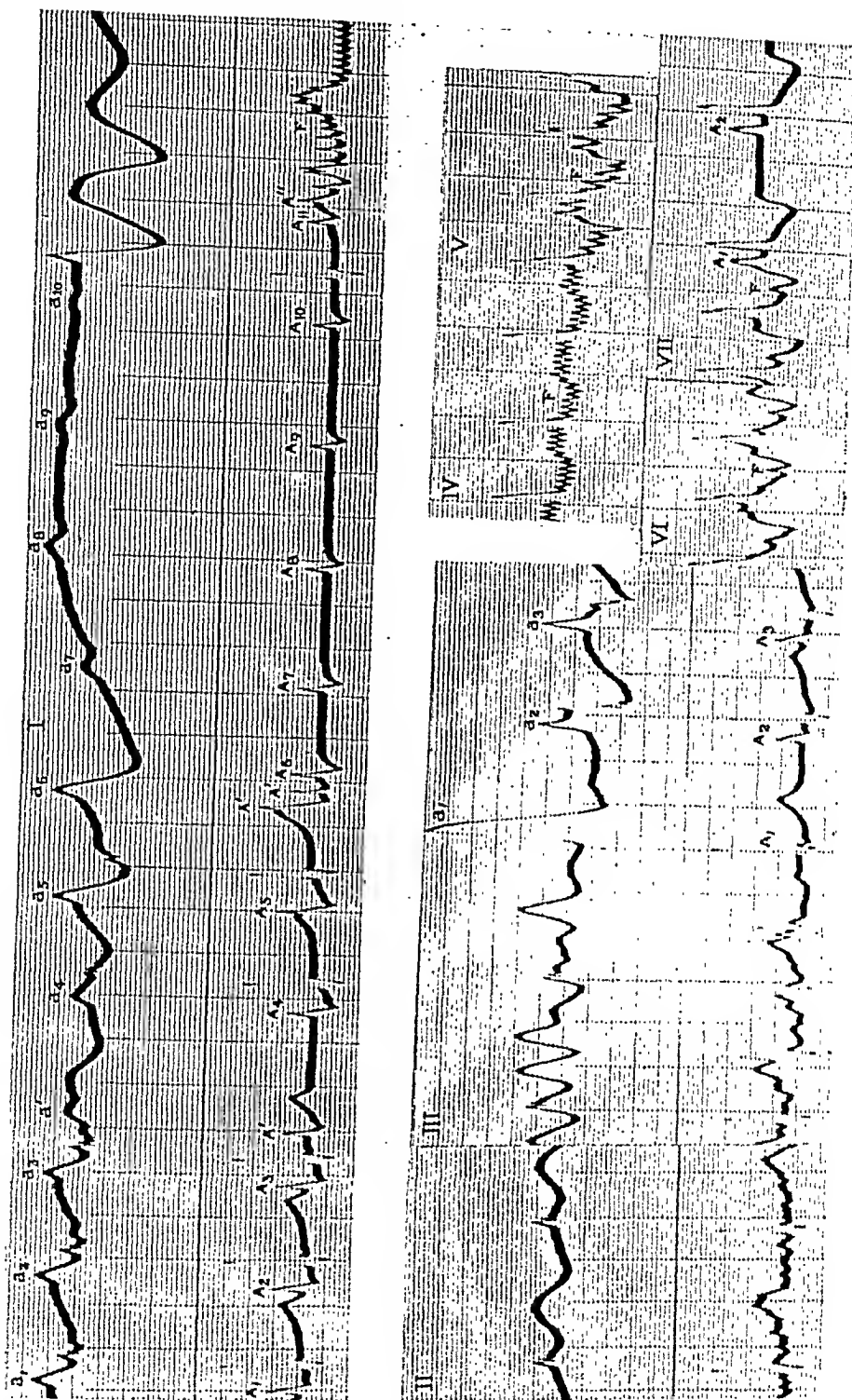


Fig. 2.—The occurrence of auricular fibrillation after the administration, intravenously, of acetylcholine to cats.  $a_1, a_2$ , etc., result from the rise in pressure caused by regular auricular contraction; and  $a'_1$ , a rise in pressure caused by an auricular premature beat.  $A_1, A_2$ , etc., represent auricular electrograms, and  $F'$ , waves of fibrillation. I, II, and III were taken from the same experiment. The tip of the cannula lay in the auricle, just beyond the entrance of the superior vena cava. I starts nine seconds after the injection of 2.5 mg. of acetylcholine, and shows a decrease in the vigor of auricular contraction ( $a_2, a_3$ , and  $a_{10}$ ), great shortening of the auricular regression process ( $A_1-A_{10}$ ), heart block following  $A_2$ , and auricular fibrillation following  $A'_1$ . II starts one minute after injection. III starts two minutes after injection. It shows the cessation of auricular fibrillation; the first normal auricular beat,  $A_1$ , is superimposed on a ventricular complex. It consequently produces a large rise in pressure,  $a_1$ .  $A_2$  and  $A_3$  are normal in contour, and give rise to normal pressure changes ( $a_2$  and  $a_3$ ) similar to  $A_1$  and  $a_1$  in I. IV, V, VI, and VII, from the same experiment, occur one, two, two and one-half, and three minutes after the injection of 2 mg. of acetylcholine. The abnormal rhythm is more in the nature of flutter (the waves remained regular); the decrease in rate can be easily followed, therefore, as the effect of the drug wears off. In VII, normal rhythm is resumed.

(Fig. 2 *I*, *A'*), and, if the dose has been large, one of these may initiate an attack of auricular fibrillation (Fig. 2 *I*, *A''*). This invariably starts as a series of rapid regular oscillations (state of rapid re-excitation) which sometimes are almost like those of alternating current (Fig. 2 *I* and *IV*, but, at other times, in each cycle, a more rapid and a slow component can be made out; these correspond to the accession and regression deflections. During the early stages of the attack ventricular contractions are infrequent, possibly because of the ineffectiveness of such small and rapid auricular stimuli, but more probably because of the coincident occurrence of auriculoventricular heart block. Then a stage usually occurs wherein the fibrillation waves are smaller and less regular (Fig. 2 *II*). As the effect of the drug wears off, the waves become coarser, until a state of impure flutter is reached; this finally gives way to normal rhythm (Fig. 2 *III-VII*).

Recovery from a single injection is apparently complete, but after repeated injections the heart weakens and the animal may die.

#### A-V STRUCTURES

As has been mentioned, when a sufficiently large dose is given, heart block, complete or partial, invariably occurs (Fig. 2 *I*).

#### VENTRICLES

The effects of vagus stimulation on the ventricles are similar in kind to those produced on the auricles, but much less in degree. For the first few beats after vagus stimulation is begun, the intraventricular pressure curve may increase in size as a result of the increased diastolic filling (Fig. 3 *II*) which is made possible by bradycardia. Subsequently, the beats may diminish (Fig. 3 *III*) in strength, but this diminution is never so great as in the case of the auricles. The extent of the negative inotropic effect varies greatly in different preparations.

The ventricular electrogram also shows less dramatic changes than the auricular. Shortening of ventricular systole cannot be made out with certainty, but the terminal portion of the regression deflection (*T* wave) is definitely increased in height (Fig. 3 *III*). With prolonged stimulation there is possibly slight reduction in the voltage of the accession deflection (*QRS*). Ventricular fibrillation following vagus stimulation did not occur in any of the experiments.

Acetylcholine also exerts less effect upon these chambers than upon the auricles. An unmistakable reduction in the force of contraction usually occurs within a few cycles after the administration of the drug. This is accompanied by an increase in the height of the regression deflection (*T* wave, Fig. 3 *VI* and *VII*). There is often a definite reduction in the amplitude of the accession deflection (*QRS*). Ventricular extrasystoles occur occasionally, as does ventricular fibrillation. The latter usually persists long enough to cause death.



## III.

A reduction in the intracardiac pressure pulse must indicate a negative inotropic effect unless the heart is inadequately supplied with blood or is contracting against reduced resistance. In the case of the auricles, after the administration of acetylcholine, it is inconceivable that they are inadequately supplied with blood, for both sinus bradycardia and heart block are present; the former allows adequate time for filling,

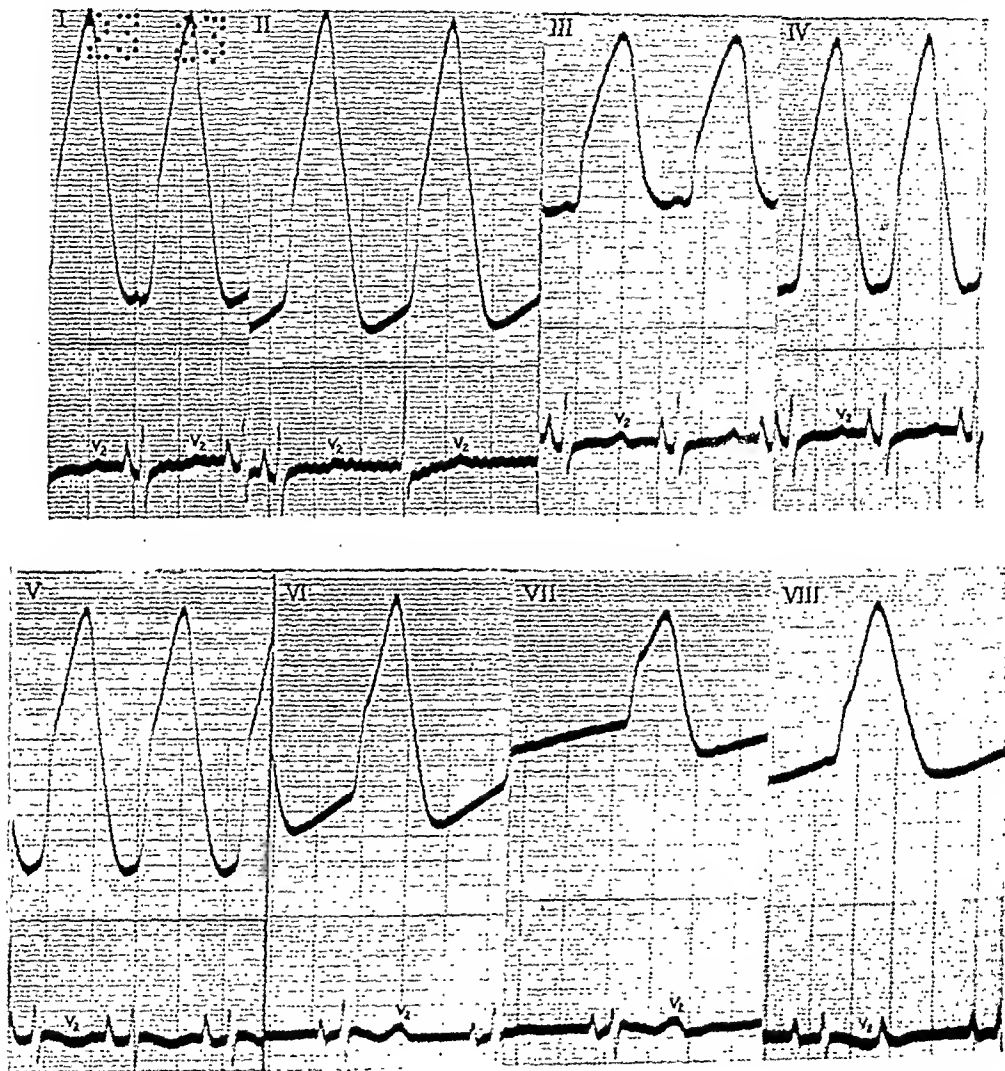


Fig. 3.—The effect of vagus stimulation and of mechoyl on the ventricles of cat.  $V_2$  represents the regression deflection (T wave) of the ventricular electrogram. All of the curves are from the same experiment. *I* was taken before vagus stimulation. *II*, one second after the start of faradic stimulation of the peripheral end of the left vagus; it shows a transient increase in the amplitude of the ventricular pressure pulse (the stimulus artifact can be seen). *III*, fifteen seconds after the beginning of vagus stimulation and five seconds after its cessation; it shows a decrease in the ventricular pressure pulse and an increase in the height of the T waves. *IV*, fifty seconds after the cessation of stimulation; it shows the return of the mechanism to normal. *V*, *VI*, *VII*, and *VIII* occur before, five seconds, forty-five seconds, and one minute, respectively, after the injection of 0.15 mg. of mechoyl. The diminution in amplitude of the pressure pulse and the increase in height of the T wave are shown. In *VIII*, heart block is present. The electrogram has returned almost to its normal form, but the pressure pulse is still smaller than the control.

and the latter retards the removal of blood. These conditions also suggest that the auricles must contract against increased, rather than reduced, resistance. If the heart rate is slow enough so that the ventricles

have been passively filled with blood before the auricles contract, the resistance against which the auricles work is the venous pressure, and this is increased. It is, therefore, certain that the reduced amplitude of the auricular pressure curve indicates a genuine, negative, inotropic effect of the drug.

The reduction in the ventricular pressure curve can be less certainly ascribed to a depressant effect on the myocardium, for, although the slow ventricular rate assures adequate filling of the ventricles, a reduction in the diastolic blood pressure could reduce the resistance against which it contracts sufficiently to account for part or all of its reduction in vigor. Following stimulation of the peripheral end of the vagus, it is not likely that much lowering in blood pressure occurs, however. The change in the shape of the electrogram indicates, furthermore, that some myocardial change has occurred. It is probable, therefore, that both vagus stimulation and the administration of acetylcholine cause some reduction in the force of ventricular contraction. Drury<sup>3</sup> failed to observe a negative inotropic effect on the ventricles as a result of vagus stimulation with the Cushman myocardiograph, but the method of investigation used in this study is probably more sensitive and might show slight changes which the older method could not detect. In any case, the ventricular effects are of a different (much smaller) order of magnitude from those which occur in the auricles.

The alterations in the electrograms indicate, accordingly, an effect on the whole heart, but predominantly on the auricles. The shortening of electrical systole in the auricles is strikingly similar to that observed by Cohn and Macleod<sup>1</sup> in the frog's heart. Although estimations of the refractory period were not made in this series, it is well known from the work of Lewis, Drury, and Bulger<sup>4</sup> that vagus stimulation reduces the refractory period of the auricles. A considerable body of evidence indicates, furthermore, that the duration of electrical systole and of the refractory period vary *pari passu*. It may be concluded, therefore, that acetylcholine reduces the duration of the active state of the mammalian auricle, as well as that of the frog.

Such a quick return to the resting stage may indicate a simple acceleration of the recovery process. If this were the case, subsequent systoles should not differ in other respects from preceding systoles. But this is not the case, for the mechanical response of these beats is greatly reduced, as is the voltage of the accession (*P*) process. In other words, rapid recovery of excitability and conductivity occurs without proper recovery of the ability to contract. Except for a reduction in the length of electrical systole, a similar dissociation of the different functions of muscle occurs in the case of calcium deficiency (Mines<sup>5</sup>).

If the views of Macleod<sup>6</sup> are correct, an altered state of recovery would be expected to affect the voltages developed during activation. The reason for this inference is that, if the constitution of resting muscle

differs from normal, so, in all probability, does the potential difference between it and active muscle. Conversely, if this potential difference is less than normal, as it is after the administration of acetylcholine, it follows that resting muscle (under its influence) is less different from active muscle than is normal resting muscle; it has incompletely recovered. An increase in the duration of the excitation process (QRS interval) could also cause a reduction in the voltage which is developed, but no significant change in the duration of this process occurs.

No shortening of the electrical response in the ventricle is observed, but there is a definite increase in the height of the regression deflection (T wave). Such a change in the form of the T wave can be accounted for only by alteration in the course taken by the spread of complete recovery, i.e., a local alteration in the duration of electrical systole. It cannot now be demonstrated whether this particular local alteration results from an increase in duration in one locality or a decrease in another. The course of events in the auricle makes the latter seem the more likely, however.

Auricular fibrillation occurs frequently after the administration of acetylcholine. After electrical systole and, of course, the refractory period have been shortened, an extrasystole nearly always gives rise to a series of ectopic beats and frequently initiates an attack of fibrillation. This arrhythmia usually persists until the effect of the drug has worn off to a considerable extent. The occurrence of these paroxysms is probably to be accounted for by a reduction in the duration of the refractory period of the auricles, which facilitates the occurrence of circus rhythm.

Ventricular fibrillation occurred in two of the twenty-eight experiments. The doses of acetylcholine were not larger than those which are usually used. In both cases it persisted long enough to cause death. Since fibrillation of the ventricles is usually attributable to something which alters their refractory period, it is probable that the occurrence of this aberrant rhythm is additional evidence that the drug produces shortening of the refractory period in that part of the ventricles which it affects. The occurrence of this irregularity in cats and dogs under the circumstances of these experiments suggests that a large dose may induce it also in patients.

The most extensive clinical use of acetylcholine and its derivatives has been in the treatment of attacks of paroxysmal tachycardia. Since they have a strong effect on the auricles and only a weak one on the ventricles, it would be surprising if they were not much more efficacious in relieving paroxysmal tachycardia of auricular, than of ventricular, origin. This does, in fact, seem to be true in the few cases of ventricular paroxysmal tachycardia so treated which have been reported. Two patients with, presumably, ventricular paroxysmal tachycardia who were treated by Starr<sup>7</sup> were not relieved by the drug; nor, in a case

reported by Harvey<sup>8</sup> was acetylcholine efficacious. In the two cases reported by Stern,<sup>9</sup> mechohine was used, but without benefit.

It is probable that the beneficial effect of the drug in cases of paroxysmal tachycardia depends on its ability to shorten the refractory period, but quinidine, which is also useful in the treatment of this condition, has an opposite effect; it lengthens the refractory period. A similar paradox was noticed by Wilson and Wishart<sup>10</sup> in their study of the intravenous use of digitalis, which also shortens the refractory period, for the relief of paroxysmal tachycardia. They concluded that these drugs apparently terminate attacks in different ways unless they possess a common effect on a still unknown property of cardiac muscle. This alternative probably does not apply in the case of acetylcholine and quinidine, because, as Starr<sup>11</sup> has found, quinidine opposes the cardiac action of acetylcholine in animals, and, in patients, a previous dose of quinidine nullifies the effect of acetylcholine on paroxysmal tachycardia. The beneficial effects of the two drugs depend, therefore, on opposite properties.

To explain these contradictory effects it becomes necessary to conclude that the desired result is obtained, not by shortening, lengthening, or adjusting the refractory period to some optimal length, but as a mere consequence of changing it. If the refractory period changes, for example, more rapidly than the abnormal mechanism can adjust itself to the new circumstances, the aberrant rhythm will cease. In this connection it is noteworthy that the most effective drugs for this purpose act rapidly and are quickly eliminated. Digitalis is not an exception to this statement, for it seems to be effective only when a large dose is given intravenously. The prophylactic effect of quinidine may depend on the fact that a constant waxing and waning of the refractory period makes the establishment of an abnormal rhythm difficult. On this assumption, a choline derivative with a slower and more prolonged action would be less, rather than more, useful.

The effect of acetylcholine on the mammalian heart is, as this study shows, purely vagomimetic. Although its effect is more intense than that of stimulation of the peripheral end of the severed vagus, it is qualitatively similar. The failure of the drug to have as pronounced an effect on the ventricles as on the auricles is of particular interest.

If the effect of the drug were exercised directly on the myocardium, the ventricles should be as greatly affected as the auricles. If the drug acts not upon the muscle itself, but upon the vagus endings, this selective action is understandable, for it is well known that the ramifications of the vagi reach nearly all parts of the auricles, but only the upper part of the ventricles. This idea is supported by the fact that the frog's ventricle, which is well supplied with vagus endings, is as much affected by the drug as the auricle,<sup>1</sup> and by the observation of Cohn<sup>12</sup> that acetylcholine has no effect upon the chick embryo heart before vagus fibers have grown into it. Since Starr<sup>11</sup> has cast grave doubt on Dale's<sup>13</sup> concept that acetyl-

eholine is effective after the vagus endings are paralyzed, it is probable that acetylcholine is not the effector substance elaborated by the vagus endings, but merely a substance capable of stimulating these endings.

#### CONCLUSIONS

By recording simultaneous intracardiac pressure pulses and electrograms, it has been shown that the effect of acetylcholine on the auricles is to reduce the force of contraction and the duration of the excited state, and frequently to produce fibrillation; it has a similar, but much slighter, effect on the ventricles. It is probable that it is more effective in auricular than in ventricular tachycardia and that it is of benefit in this condition because it changes the refractory period rapidly, rather than because it shortens it. It acts on the vagus endings, rather than on the muscle proper.

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## CONTRAST ROENTGEN VISUALIZATION OF COARCTATION OF THE AORTA

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THE roentgenologic diagnosis of coarctation of the aorta is based ordinarily upon indirect evidence, since the narrowed and the adjacent segments of the aorta often are difficult or impossible to demonstrate. Notching of the caudad edges of the ribs posteriorly is most characteristic but is demonstrable only occasionally. Changes in the cardiac silhouette due to left ventricular hypertrophy may occur. The size and pulsations of the aorta proximal to the coarctation vary and are of no definite value in differential diagnosis. In children particularly, these roentgen findings are difficult to demonstrate. The method of Robb and Steinberg<sup>1</sup> provides direct visualization of the great vessels and their branches as well as of the cardiac chambers. Hence it should be applicable to the elucidation of clinically obscure or atypical instances of coarctation. This possibility is referred to by Robb and Steinberg.<sup>2</sup>

In the following two cases coarctation of the aorta was suspected clinically. Demonstration of the actual coarctation and its precise localization was accomplished by contrast visualization. The fluorographic method described previously<sup>3</sup> was used in order better to identify the cardiac chambers and the aorta.

### CASE REPORTS

CASE 1.†—19570. E. M., a twelve-year-old boy, was seen in the Out-Patient Department of the Mount Sinai Hospital (service of Dr. Béla Schick) for the first time on March 16, 1940. He was and had been perfectly well except for childhood diseases. Seven months previously he was examined by a school physician who discovered cardiac murmurs and diagnosed rheumatic heart disease. For this reason the patient entered the clinic for examination.

Physical examination revealed the boy to be healthy in appearance though somewhat underdeveloped. The heart was enlarged to the left, the cardiac dullness reaching beyond the nipple line. There was a loud blowing systolic murmur over the lower right border which radiated to beneath the right scapula. A loud blowing diastolic murmur was heard over the second intercostal space and to the right of the sternum. This was transmitted to the neck.

Blood pressure determinations were as follows: Left arm 160/98; right arm 158/98; left leg 98/84; right leg 96/80.

Urine examination showed no albumin or sugar; the microscopic examination did not reveal any abnormalities.

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†The complete clinical data on this case are included in a forthcoming publication by S. Blumenthal and D. Davis, "Coarctation of the Aorta."



Fig. 1.—Case 1. White arrow points to coarctation. Black arrow points to aortic valve. There is considerable dilatation of the left ventricular cavity and the supra-cardiac portion of the aorta. There is marked dilatation of the arteries of the neck. The descending aorta is of normal caliber below the coarctation.



Fig. 2.—Case 1. The heart and large vessels are magnified because the patient moved away from the fluoroscopic screen during the exposures. However, arrow points to visualized right internal mammary artery.

Electrocardiographic examination showed no other abnormalities; there was no axis deviation.

A roentgenogram of the chest showed a somewhat enlarged heart which was globular in shape. The descending aorta was not visualized successfully. No abnormality was noted in the ribs.

*Comment.*—In this case, the clinical diagnosis of coarctation of the aorta was based upon the presence of a classical clinical picture. Corroborative roentgen evidence was lacking. Contrast visualization demonstrated the narrowed segment in the proximal descending aorta, a normal aorta immediately proximal and distal to the coarctation, moderate dilatation of the ascending aorta particularly in the supracardiac portion, and left ventricular dilatation and hypertrophy. There was a peculiar variation in the density of the ascending aorta, the significance of which was not determined. The dilated right internal mammary artery was also seen (Figs. 1 and 2).



Fig. 3.—Case 2. Left oblique position. Visualization of the right auricle and right ventricle which are normal in appearance. The pulmonary artery is dilated. The interventricular septum reaches more to the right than usual because of enlargement of the left ventricle.

CASE 2.—L. C., 456241, a 23-year-old Jewish housewife, entered The Mount Sinai Hospital, service of Dr. B. S. Oppenheimer, on May 6, 1940, complaining of loss of weight, palpitation and neck enlargement during the previous two months. She had always been in good health but had been irritable, excitable and nervous. She had no headaches nor any cardiovascular symptoms. Two years previously her blood pressure, taken by a physician, was said to have been normal. Two months



previous to admission when she began to perspire easily, lose weight and experience palpitation, a physician found a markedly elevated blood pressure.

Physical examination showed moderate exophthalmus, lid lag and stare. The fundi revealed changes consistent with myopia. The thyroid was enlarged diffusely and a bruit was heard over it. The heart was enlarged to the left and a loud, high pitched systolic murmur was heard at the apex and over the pulmonary area which radiated to the back and lumbar region.  $P_2$  was greater than  $A_2$ . The heart rate was 120-130 per minute, the rhythm regular. No intercostal pulsations were noted. There was a fine tremor of both hands. Repeated blood pressure determinations in both arms averaged 220/100; in the legs 120/100.



Fig. 4.—Case 2. Left oblique position. The arrow points to coarctation. The left ventricular cavity is small. There appears to be marked hypertrophy of the left ventricular wall. The arteries of the neck are dilated.

Laboratory Findings. Hemoglobin 83 per cent, W.B.C. 8,300, polymorphonuclear leucocytes 21 per cent, monocytes 4 per cent, eosinophilic leucocytes 1 per cent. Urine examination: specific gravity 1.030, albumin faint trace; microscopic, occasional R.B.C. and W.B.C. Blood Chemistry: Urea N, 8 mg., sugar 90 mg., cholesterol 220 mg. per 100 c.c. Blood Wassermann was negative. Basal metabolic rate was +52 per cent and +43 per cent on separate occasions. The patient was given Lugol's solution and the basal metabolic rate fell progressively to +17 per cent. The sleeping pulse rate ranged between 104 and 120 per minute.

Circulation studies: Venous pressure 14 cm.; saccharine time 5 seconds.

Blood flow studies:

Left arm—32° C.—37 c.c./per min. per c.c. of arm volume.  
42° C.—60 c.c./per min. per c.c. of arm volume.

Right foot—32° C.— 7.1 c.c. per min. per c.c. of leg volume.  
42° C.—22.6 c.c. per min. per c.c. of leg volume.

ECG: Sinus tachycardia, rate 130 per minute. Left axis deviation. QRS of high voltage. R-T depressed slightly in Leads II and III. These evidences indicate left ventricular enlargement.

X-ray examination of the chest: "Heart enlarged to the left; the 4th and 5th and 6th ribs show a slight notching of their inferior surfaces at the postero-axillary line. The lungs show no abnormality. Roentgenkymogram shows marked irregularities in diastole and some diminution in pulsations at the apex and supra-apical area of the left ventricle. Pulsations of the aortic arch are within normal limits. There appears to be some diminution in the pulsations transmitted to the esophagus in the region of the lower thoracic aorta."



Fig. 5.—Case 2. Lateral view. Arrow points to coarctation. The ascending and descending aorta on either side of the coarctation are of normal caliber.

*Comment.*—The presence of extreme hypertension, cardiac murmurs, lowered blood pressure in the legs, differences of blood flow in the upper and lower extremities, absence of findings pointing to renal disease and the roentgen finding of notched ribs suggested the diagnosis of coarctation of the aorta. However, the history of a normal blood pressure before the onset of the present illness was, to say the least, disturbing. The coexistence of Graves' disease also led to considerable confusion. Contrast visualization was therefore of utmost importance. A narrowed segment of the aorta was demonstrated in the pars descendens distal to the exit of the left subclavian artery. The left ventricle was markedly hypertrophied, the ventricular cavity being relatively small. The supracardiac portion

of the aorta was dilated. The right ventricle was of normal size but the pulmonary artery appeared irregularly dilated.

#### SUMMARY

1. Contrast visualization of the aorta offers an excellent diagnostic aid in clinically obscure or atypical cases of coarctation of the aorta.
2. The fluorographic multiple exposure technique is especially advantageous, since many photographs with fluoroscopic observation of the required phase of the cardiac cycle are obtained.
3. There has been no undue reaction to the necessary procedures, whether in children or in adults.

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# BALL THROMBI IN THE HEART

## REPORT OF THREE CASES

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THE first observation of a ball thrombus in the heart was published by William Wood<sup>1</sup> in 1814. The condition is rare, the literature containing reports of 31 cases.<sup>2</sup> Reviews of the literature have been made by Welch<sup>2</sup> (1899), Hewitt<sup>3</sup> (1916), Abramson<sup>4</sup> (1924) and Aronstein and Neuman<sup>5</sup> (1939).

Ball thrombi are so called because of their spherical or ovoid shape and their lack of attachment. The diameter has varied from 1 to 4 cm. and has been greater than that of the orifice of the chamber in which the thrombus lay. The color has been various shades of gray, red and brown and the surface has been either smooth or rough. Some have shown central softening; others were solid, occasionally with lamination. In the authentic cases the ball thrombus has been located in the left atrium and mitral stenosis has been present. These general characteristics are summarized by Welch<sup>2</sup> as follows:

"(1) entire absence of attachment and consequent free mobility; (2) imprisonment in consequence of excess in the diameter of the thrombus over that of the first narrowing in the circulatory passage ahead of it; and (3) such consistence and shape that the thrombus must not of necessity lodge as an embolus in this passage. The third point does not prejudice the question of the possibility of a ball-thrombus lodging as an embolus; but it excludes from the group . . . detached, shaggy, irregular masses . . . as must necessarily be caught at once as emboli in the narrowed passage in front."

Mitral stenosis is important in the production of ball thrombi in that it is often associated with auricular mural thrombi, portions of which may become detached and then held back by the narrowed orifice. Auricular fibrillation, usually present in cases of ball thrombi, is another important factor in that it favors the formation of mural thrombi and perhaps their detachment. Auricular fibrillation also causes incomplete emptying and a tendency to rotary motion of the blood in the atria, factors which interfere with the lodgement and fixation of thrombotic masses in the valve orifice.

In some instances a rough or projecting spot on the thrombus has indicated its previous point of attachment and also its recent separation. Thus certain ball thrombi have had a spherical shape while still attached. No doubt in other instances irregularly shaped bits of mural thrombi have become detached and have rotated about, growing by

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successive accretions and assuming a spherical shape by a process of moulding and grinding.

The clinical diagnosis of a ball thrombus is difficult. Usually there have been no symptoms suggestive of its presence. In the few cases in which an antemortem diagnosis has been made or considered, there has been widespread and more or less transient interference with the peripheral circulation in a case of mitral stenosis with auricular fibrillation.<sup>6</sup> This phenomenon is presumably due to intermittent partial obstruction of the mitral orifice. Exceptionally, the ball thrombus has caused sudden death. Embolic phenomena have occurred in most of the cases.

Three cases of ball thrombi have been encountered at Cleveland City Hospital in 6,285 consecutive autopsies performed from January 1, 1930, to July 1, 1939, inclusive. This group of autopsies included 156 cases in which rheumatic heart disease was the principal or an important contributory cause of death, an incidence of one case of ball thrombus in 52 autopsy cases of rheumatic heart disease.

CASE 1.—M. L., a white female aged 48, was admitted to Cleveland City Hospital June 24, 1934, for a dilatation and curettage because of symptoms suggestive of a uterine carcinoma. In addition, she had had several "fainting spells" and had become fatigued easily, during the past few years.

General physical examination showed nothing remarkable. The cardiac mechanism was normal except for premature contractions, and no murmurs were heard. There were no signs of myocardial insufficiency and the patient was considered to be a normal risk for anesthesia.

On June 28, a dilatation and curettage was performed. The biopsy material did not show carcinoma. The patient's immediate postoperative course was normal.

On the sixth postoperative day, July 4, 1934, the patient complained of severe pain in the legs. The arteries of the legs could not be felt to pulsate. The cardiac mechanism was now auricular fibrillation. During the following few days, ischemic necrosis of the right foot and the distal portion of the right leg appeared. The left leg was pulseless but did not show ischemic necrosis. The patient died July 8, 1934, the clinical diagnosis being auricular fibrillation of obscure etiology and ischemic necrosis of the right foot and right leg due to an embolus which had lodged at the bifurcation of the aorta causing complete obstruction of the right iliac artery and partial obstruction of the left iliac artery.

*Autopsy Findings.*—(Autopsy No. A 9611, performed by Dr. D. J. Rehbock, eighteen hours after death.) The heart showed a rheumatic tricuspid stenosis of moderate degree and a severe mitral stenosis, the diameter of the orifice being 1.3 cm. The left auricular appendage was large, and attached to the wall was a thrombus of irregular shape which measured 6 by 2.5 by 2.5 cm. in size. Lying free in the dilated left atrium was a roughly spherical, fairly smooth surfaced thrombus which measured 3 cm. in diameter. Both thrombi were grayish-brown in color and showed central softening and liquefaction.

The distal portion of the aorta was almost completely occluded by an embolus. The right foot and distal part of the right leg showed ischemic necrosis. There were several moderately large infarcts in the spleen and the right kidney.

Microscopically the thrombus attached to the wall of the left auricle was well organized in its deeper portion. The ball thrombus showed a thick peripheral area of dense homogenous basophilic unorganized material. The aorta showed a large, partially depigmented unorganized thrombus attached to the intima.

CASE 2.—S. C., a white female aged 86, entered Cleveland City Hospital April 19, 1935, with a complaint of pain in the right foot of six days' duration. For the past two years the patient had had increasingly frequent attacks of unconsciousness of short duration. Two weeks prior to admission she became orthopneic and noted palpitation. The pain in the right foot had been sudden in onset, constant and severe. The foot had turned a bluish-black color the day of admission.

Examination showed the patient to be dyspneic. There were râles at the bases. The heart was enlarged and the cardiac mechanism was auricular fibrillation with an apical rate of 192 beats per minute. No murmurs were distinguishable. The liver was enlarged. The right foot showed early ischemic necrosis and the right femoral, right popliteal and right dorsal pedis arteries could not be felt to pulsate. The arteries of the left leg could be felt to pulsate. The arteries in general showed evidence of moderate arteriosclerosis.

The patient's condition became poorer and she died May 4, on the fourteenth hospital day. The clinical diagnosis was generalized arteriosclerosis, coronary artery sclerosis, cardiac hypertrophy, myocardial insufficiency, auricular fibrillation, and an embolus in the right femoral artery with ischemic necrosis of the right foot.

*Autopsy Findings.*—(Autopsy No. A 10008, performed by Dr. G. W. Hobson, six hours after death). The heart showed moderately severe coronary arteriosclerosis and myocardial sclerosis, but in addition there was a severe rheumatic mitral stenosis, the diameter of the orifice being 1.6 cm. The left atrium contained an irregular surfaced, yellowish-pink, soft centered, spherical thrombus which measured 2.2 cm. in diameter. No mural thrombi were present at any point.

The various arteries showed rather severe arteriosclerosis. The right femoral and right popliteal arteries were thrombosed. Whether this was of embolic origin or whether it had originated in situ could not be determined. The right foot showed ischemic necrosis.

CASE 3.—D. B., a white male aged 46, was admitted to Cleveland City Hospital January 24, 1938, with the complaint of "heart trouble." On previous admissions in 1928 and in 1934, the diagnosis was mitral stenosis, auricular fibrillation and a cerebral embolus.

Examination showed the typical signs of mitral stenosis and auricular fibrillation. There was evidence of mild myocardial insufficiency and signs of consolidation in the lower lobe of the left lung, interpreted as infarction.

The patient improved quickly on appropriate treatment and was discharged February 11, 1938. While walking through the ward on his way out of the hospital he fell dead. It was thought that a pulmonary embolus was the cause of death.

*Autopsy Findings.*—(Autopsy No. A 11999, performed by Dr. T. B. Keller six hours after death.) The heart showed a severe rheumatic mitral stenosis, the orifice averaging 6 mm. in diameter. A fairly smooth surfaced, ovoid shaped thrombus measuring 2 by 2 by 4 cm. was wedged into the mitral orifice so as to cause complete obstruction. In the left auricular appendage there was a short stock-like mural thrombus which measured 5 mm. in diameter. The ball thrombus possessed a pedicle, the structure of which was similar to that of the mural thrombus. In the cavity of the left ventricle there was a small thrombus which had become detached from the ball thrombus.

The other important postmortem findings included recent and remote bilateral infarcts of the lungs, and remote infarcts of the brain, spleen and kidneys.

#### COMMENT

In Case 1 it is debatable whether or not the ball thrombus caused symptoms. The attacks of syncope may have been due to transient cerebral ischemia caused by temporary obstruction of the mitral orifice, but that point is highly speculative since the patient was not examined during such an attack. The ball thrombus itself was typical in appearance and in the circumstances under which it occurred, i.e., in the left atrium in a case of mitral stenosis with auricular fibrillation.

Again in Case 2 the transient attacks of unconsciousness may or may not have been due to the ball thrombus intermittently obstructing the mitral orifice. The ball thrombus in this case was typical in regard to appearance and the conditions under which it occurred. The patient's age, 86, is noteworthy. The oldest age previously recorded in a case of ball thrombus is 55 years.<sup>5</sup>

In Case 3 the ball thrombus caused the patient's sudden death by wedging into the mitral orifice. In its location and in regard to the circumstances under which it occurred, the thrombus was typical of a ball thrombus.

#### SUMMARY

Three ball thrombi have been encountered in 156 consecutive autopsies in which rheumatic heart disease was the principal or an important contributory cause of death. Rheumatic mitral stenosis with auricular fibrillation was present in all three cases. The ball thrombi occurred in the left atrium. It cannot be determined whether the ball thrombi were the cause of attacks of syncope which two of these patients suffered. The third patient died suddenly. At autopsy a smooth ovoid shaped thrombus was found wedged into the stenosed mitral orifice.

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## Department of Clinical Reports

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### BULLET WOUND OF THE HEART, WITH CORONARY ARTERY LIGATION

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INSTANCES of bullet or knife wounds of a coronary artery, in which the patient is operated upon and survives, are rare enough to justify reporting. Even wounds produced by a needle may prove fatal.<sup>1</sup> The increasing frequency of heart wounds is indicated by the fact that two series of more than twenty cases have been reported by Elkin<sup>2</sup> and Bigger<sup>3</sup> during the past decade. These surgeons, together with Beck,<sup>4</sup> have expounded the principles of diagnosis and treatment.<sup>5</sup>

#### CASE REPORT

R. W. (U-82423), a 27-year-old colored man, was admitted to the Cincinnati General Hospital at 10:19 P.M. on Nov. 15, 1937, ten minutes after being shot in the chest. He was pulseless and comatose. He smelled of alcohol and at times thrashed about wildly. Examination revealed a sturdy negro in profound shock, with cyanosis and a cold, sweating skin. The respirations were rapid and shallow. There was a bullet wound, almost in the midline, at the level of the fourth intercostal space. The muffled and distant heart sounds could be heard only at the left sternal border, but the rhythm was normal. The cardiac dullness was increased a little at the base. No evidence of pneumothorax or hemothorax was found. The jugular veins stood out like cords. The venous pressure (direct method) was more than 36 cm. of water. The abdomen was soft, but apparently slightly tender below the left costal margin. The patient vomited several times, but the vomitus did not contain blood.

Acacia and saline (500 c.c.) were administered intravenously, and the pulse became palpable. The systolic blood pressure varied from 60 to 80 mm. Hg, and a marked paradoxical pulse was noted both by palpation and auscultation. A roentgenogram showed that the bullet was apparently just beneath the diaphragm. No air could be seen below the diaphragm, but the patient had been lying flat. The heart was not enlarged. Fluoroscopic examination was not attempted.

Because the signs of tamponade indicated that the cardiac condition was more perilous than any possible abdominal injury, his chest was opened. The operation was performed by Dr. Josiah H. Smith. The following is a résumé of his note.

The incision was made under local novocain anesthesia. The third, fourth, and fifth costal cartilages and a portion of the sternum were removed. The left medial reflection of the pleura was pushed laterally. The pericardium was blue, tense, and pulsated very little. Upon opening it, about 600 c.c. of blood gushed out. The systolic blood pressure immediately rose to 110, and the patient recovered consciousness.

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The heart was then delivered into the wound. The anterior descending branch of the left coronary artery had been severed by the bullet, and this accounted for the major portion of the bleeding. A laceration of the heart was found on the anterior surface about 1.5 cm. above the apex, just medial to the severed artery (i.e., to the patient's right). Bleeding was controlled by the finger. The ventricle had not been punctured. A stay suture of medium black silk was placed through the apex of the heart.<sup>4</sup> The bleeding coronary artery was ligated. The rent was closed with three interrupted sutures without disturbing the endocardium. During the manipulation the heart beat became irregular and the systolic blood pressure fell to about 60. This necessitated releasing the traction suture on several occasions, which was followed by restoration of normal rhythm and return of the blood pressure to 110.

The pericardium was loosely closed with interrupted sutures of medium black silk, leaving room for drainage. A small wick was inserted underneath the muscles, but not down to the pericardium. A 150 c.c. transfusion was given during the operation.

*Postoperative Course.*—The patient stood the operation well, and immediately after it the paradoxical pulse had disappeared. There were occasional premature beats. The abdomen remained negative. An electrocardiogram was taken at 2 A.M. on Nov. 16, less than two hours after the coronary artery was tied.

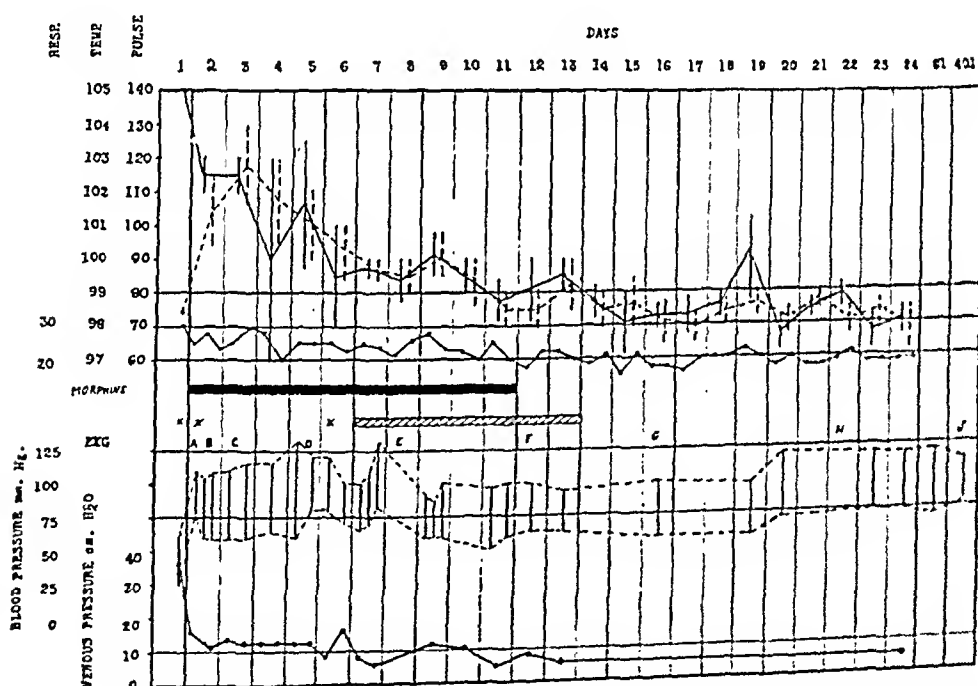


Fig. 1.—Record of the temperature, pulse rate, respiration, arterial blood pressure, and venous pressure, before and after operation. The X's indicate transfusions. The letters refer to the electrocardiograms in Fig. 2. The cross-hatched line indicates days when aminophyllin was given. In the temperature (---) and pulse (—) curves, the daily fluctuations are recorded and the means are connected. The period of tachycardia on the nineteenth day followed smoking.

The course of events can be followed by referring to the chart (Fig. 1). He was given transfusions of 500 c.c. and 250 c.c., as indicated. Morphine was used to keep him quiet, and, after four stormy days, his condition improved steadily. He experienced no chest pain. No pericardial friction rub was heard and no murmur appeared, although he was examined repeatedly. When the drain was removed from the wound thirty-six hours after operation, about 30 c.c. of serous fluid spouted

out synchronously with the heart beat. There was some drainage for the next two days. Thereafter the wound healed uneventfully. Pulsus paradoxus was present during the first week. On the sixth postoperative day the administration of aminophyllin was begun; 21 grains were given daily for a week.<sup>6</sup> On the third postoperative day his pulse rate fell suddenly from 120 to 60, but no electrocardiogram was taken. Once, after smoking, he became alarmed because of palpitation and tachycardia. Subsequently, a tracing was made before and after he smoked two cigarettes. The rate increased from 74 to 105 per minute and the number of extrasystoles decreased temporarily, but there were no other changes. Extrasystoles were continuously present after the operation. There were no embolic phenomena.

*Subsequent Course.*—He was discharged Jan. 28, 1938, ten and one-half weeks after admission, and advised to rest at home. When he was seen in the surgical clinic Feb. 21, his heart was of normal size, as shown by percussion and roentgenologic examination. He had mild dyspnea on exertion, but no edema. He complained of a stinging pain, at times, which started over his heart and radiated down the left arm to the elbow. The pain occurred only when he was lying down, never upon exertion. Olm and Hughes<sup>7</sup> have pointed out that pain may be absent in such cases because of interruption of the periarterial nerve plexus. Since pain does not occur in some cases of acute coronary obstruction and myocardial infarction, especially in negroes,<sup>8</sup> such cases as this throw little light on the mechanism of its production or reasons for its absence. It has been reported in cases of wound of the heart.

The patient was readmitted for study Dec. 10, 1938, thirteen months after the injury. He had rested during February and March, and possibly thereafter, for he was employed on a Works Progress Administration project. He had no dyspnea, edema, pain, or any other trouble, except that occasionally, when quiet, his heart would "jar" him. A soft systolic murmur was heard at the apex. Extrasystoles occurred every three or four beats. Fluoroscopic study revealed that the left ventricle was slightly enlarged. There was no evidence of pericardial adhesions or constriction. The bullet was far anterior, just in front of the extreme left portion of the apex. The vital capacity was 93 per cent of normal (McKesson-Scott), and the circulation time, with 5 c.c. of 20 per cent decholin, was 16 seconds (normal).

When last heard of, in February, 1940, he was doing manual labor for a railroad and had no symptoms or disability.

#### DISCUSSION

In none of Elkin's, and in only two of Bigger's twenty-five cases, was the heart wound caused by a bullet. One patient with a superficial wound of the right ventricle recovered. In the other, the "bullet had destroyed a rather large segment of the left border of the heart, including anterior, left lateral, and posterior walls of the left ventricle." Victims of such a wound probably rarely obtain any benefit from surgical procedures. Certain ideal circumstances must prevail in order that a patient with a bullet wound may survive. The path must be such that the integrity of no large area of the myocardium is disrupted. Hemorrhage must not be severe, or must be controlled promptly. Other vital organs must escape lethal damage. What the phase of the cardiac cycle may be makes a difference, for a bullet which could kill in diastole might inflict only slight damage if it struck during systole. Similarly, respira-

tion might alter the position of the heart. Such requirements demand nice precision upon the part of a bullet if it is to wound but not kill. Recovery from *bullet* wounds of the heart is rare because of the infrequent conjunction of so many necessary conditions.



Fig. 2.—Serial electrocardiograms (see also Fig. 1).

Record A, taken two hours after operation

Record B, ten hours after operation

Record C, on the third day

Record D, on the fifth day

Record E, on the eighth day

Record F, on the twelfth day

Record G, on the sixteenth day

Record H, on the twenty-second day

Record I, on the forty-first day

Record J, one year and five weeks after operation

Roman numerals indicate leads. In record J the Lead IV was taken in accordance with the recommendations of the American Heart Association.<sup>7</sup>

I have found only two cases of heart wounds in which chest leads were made.<sup>5, 9</sup> In one case<sup>9</sup> they were first employed on the fourteenth day after operation, and, in the other,<sup>5</sup> on the thirteenth day. Un-

doubtedly the wound usually is not disturbed during the early post-operative course. Increased movement of the precordium may lead to artifacts (see Record A), as was pointed out by Davenport, Blumenthal, and Cantril.<sup>9</sup> In our case we obtained a chest lead two hours after the operation, on the second day, and regularly after the fourth day. The entire group is not included because it would take too much space, but all of the essential changes are shown in Fig. 2. Unfortunately, the condition of the patient did not permit us to obtain tracings before operation.

#### ELECTROCARDIOGRAPHIC CHANGES (FIG. 2)

Record A, taken two hours after operation, reveals multiple ventricular extrasystoles originating in the region of the apex of the left ventricle.  $T_1$  and  $T_4$  are diphasic, but the  $T_4$  change may have been caused by movement of the precordium.<sup>9</sup> (It is possible that there is a 2:1 A-V block in this lead, with the P waves buried in the T waves.)  $T_2$  and  $T_3$  are high. S- $T_{1,2,3}$  are all distinctly, although slightly, elevated. The axis is normal. A very small  $Q_4$  is present.

Record B was taken eight hours after record A. The QRS complex in Lead I is splintered. S- $T_1$  is now clearly elevated, and the T wave has lost its upward convexity. In Lead II a Q wave has appeared, the T waves have decreased in amplitude, and the S-T take-off is more elevated. In Lead III a definite Q wave has appeared, and the S-T take-off is almost isoelectric. The voltage has decreased in all leads.

Record C, taken thirty-four hours after operation, shows a high take-off of S- $T_{1,2,3}$  which suggests pericarditis.<sup>10</sup> There is a tendency toward left axis deviation. In Lead IV there is slight depression of the RS-T segment, with an upright T.

Records D and E show progression of the T-wave changes.

Record F, taken twelve days after the operation, shows a lowering of the S-T take-off in Leads I, II, and III and some increase in QRS amplitude; the S-T segment in Lead IV is isoelectric and  $T_4$  is upright.

Record G, four days later, shows continued recession of the T-wave changes. The "Pardee" T waves are inverted in the three standard leads. Splintering of the small QRS complexes remains.  $Q_4$  is still present and the T wave is upright.

Records H and I, taken twenty-two and forty-one days, respectively, after operation, show further progression of changes.  $Q_1$  is a little deeper, and the T waves are sharply inverted and have characteristic conformation.<sup>10</sup> In record I, the Q wave has almost disappeared in Lead IV.

Record J, taken a year and five weeks after operation, reveals that  $T_1$  is upright.  $T_2$  is isoelectric and  $T_3$  is inverted, although not as sharply as a year before. In Lead IV (new method<sup>15</sup>) the T wave is inverted, and corresponds with stage 8 of Bohning and Katz.<sup>11</sup> The Q wave has disappeared entirely. The ventricular extrasystoles persist. A small  $Q_4$  persists.

Interpretation of these electrocardiographic changes presents difficulties. The elevation of the S-T segments in the three standard leads might be accounted for by pericarditis.<sup>10</sup> There was no positive evidence of this clinically; no friction rub was heard, and the most pronounced changes occurred in records D and E, which were taken on the fourth and fifth days, respectively, when the patient's condition was improving. Wood<sup>12</sup> has emphasized the significance of what he calls the  $T_2$

type of electrocardiogram. In contradistinction to the  $T_1$  and  $T_2$  types of anterior and posterior infarction, this variety is characterized by the fact that it shows the most prominent changes in Lead II. The S-T segment has a higher take-off than in Leads I or III. In Gissane and Schulenburg's case,<sup>13</sup> which Wood describes, there was a penetrating stab wound in the diaphragmatic (posterior), as well as in the anterior wall of the right ventricle, both of which required suture.<sup>14</sup> The three standard leads in our case are very much like others which have been reported.<sup>12, 13</sup> It is possible that the control suture which is placed in the apex to obtain stability<sup>4</sup> produces some damage.

Wolferth and Wood<sup>14</sup> have reported cases of spontaneous coronary occlusion, with anterior and posterior infarction, in which the electrocardiograms were very much like those in this series. Certainly the acute changes include much more than one might expect with uncomplicated, anterior, left ventricular infarction.<sup>5, 9</sup> Over a year after the accident (record *J*),  $T_2$  was isoelectric, and  $T_3$  was still well inverted. This is characteristically the late T-wave position in cases of posterior infarction. The changes in the chest lead were such as one would expect with anterior infarction. In record *J* the new method was used.<sup>15</sup> It shows no Q wave, but a persistent T-wave change (i.e., inversion, which corresponds to an upright T in the antecedent chest leads).

Thus, the  $T_2$  changes that are characteristic of posterior infarction and the chest lead changes which occur as a result of anterior infarction, plus a persistent  $Q_1$ , lend some weight to the assumption that both walls of the ventricle were damaged. It may be that a combination of pericarditis, operative trauma, and the bullet itself contributed to the ventricular injury. The amplitude of the QRS complexes has remained low.

The remarkable thing is that, in spite of these persistent changes in the electrocardiogram, the patient should be entirely well. Whether they herald a bad prognosis cannot be stated. The only symptom after the first three months was the annoying palpitation which is so common with extrasystoles. His cardiac function is good enough for heavy physical work.

A search of the literature<sup>2, 3, 5, 7, 9, 12, 13, 16</sup> has revealed no case in which ventricular extrasystoles were a permanent sequel of a direct wound of the heart. In the first lead in record *J* there are extrasystoles from two foci in the ventricle. They usually produced a similar deflection, however, as may be seen in Lead II. Slight differences may be accounted for by superimposition of the P wave. These beats have varied from every other beat to one out of thirty, but usually came every six to eight beats. We have no long strip of tracing which might reveal that they were of parasystolic origin.

## SUMMARY

1. Serial electrocardiograms, made after ligation of the anterior descending branch of the left coronary artery, which had been severed by a bullet, are reported. This is the third case in which chest leads were recorded after a heart wound in man.

2. Persistent ventricular extrasystoles and Q- and T-wave changes were observed, and their nature is discussed. The patient is apparently normal, in spite of persistent abnormalities in the electrocardiogram.

I wish to thank Dr. Johnson McGuire for help with the electrocardiograms, and Dr. Josiah Smith for permission to report this case.

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4. Beck, C. S.: Wounds of the Heart; Technique of Suture, *Arch. Surg.* 13: 205, 1926.
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6. Fowler, W. M., Hurwitz, H. M., and Smith, P. M.: The Effect of Theophyllin Ethylenediamine on Experimentally Induced Cardiac Infarction in the Dog, *Arch. Int. Med.* 56: 1242, 1935.
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9. Davenport, S. L., Blumenthal, B., and Cantril, S.: Electrocardiographic Studies of a Stab Wound of the Heart, *J. Thoracic Surg.* 5: 208, 1935.
10. Bellet, S., and McMillan, T. M.: Electrocardiographic Patterns in Acute Pericarditis, *Arch. Int. Med.* 61: 381, 1938.
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13. Gissane, W., and Schulenburg, B.: A Penetrating Stab Wound of the Heart, *Lancet* 2: 132, 1937.
14. Wolferth, C. C., and Wood, F. C.: Acute Cardiac Infarction Involving the Anterior and Posterior Surfaces of Left Ventricle, *Arch. Int. Med.* 56: 77, 1935.
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16. Koucky, J. D., and Milles, G.: Stab Wound of the Heart, *Arch. Int. Med.* 56: 281, 1935.

# Department of Reviews and Abstracts

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## Selected Abstracts

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Whittenberger, James L., and Huggins, Charles: Ligation of the Inferior Vena Cava. *Arch. Surg.* 41: 1334, 1940.

Ligation of the vena cava above both renal veins causes death in dogs in a few hours from surgical shock due to accumulation of blood from two kidneys, in the posterior portion of the body. When oblique ligation of the vena cava between the kidneys is done, allowing development of collateral veins in one kidney, subsequent complete high ligation of the vena cava is well borne; it is not followed by shock or interference with renal function in the kidney with adequate venous drainage.

NAIDE.

Bellet, Samuel, Kershbaum, Alfred, Meade, Richard H., Jr., and Schwartz, Leon: The Effects of Tobacco Smoke and Nicotine on the Normal Heart and in the Presence of Myocardial Damage Produced by Coronary Ligation. *Am. J. M. Sc.* 201: 40, 1941.

Experiments were performed on normal animals and on animals in various stages of myocardial infarction following coronary ligation in order to study the cardiac effects following the inhalation of tobacco smoke and nicotine injection.

It was found that normal unanesthetized animals were able to tolerate a fairly wide range of dosage with the production of only slight electrocardiographic changes. Following myocardial damage produced by coronary ligation, marked electrocardiographic changes were obtained with a dose that was one-fourth of that required to produce only slight changes in the normal animal. These changes became less marked as the subacute stage was reached and were still less evident in the chronic stage of infarction. However, the electrocardiographic changes after equivalent doses were more marked in the stage of chronic infarction than in the normal controls. The factor of tolerance was considered and was shown not to materially influence these results. Apparently, a parallel existed between the degree of the electrocardiographic effects following the administration of nicotine and the severity of the myocardial damage.

AUTHORS.

Nonidez, José F.: Studies on the Innervation of the Heart. Distribution of the Cardiac Nerves, With Special Reference to the Identification of the Sympathetic and Parasympathetic Postganglionics. *Am. J. Anat.* 65: 361, 1939.

The present article is based on observations with the chloral hydrate formula of the method of Cajal, carried out on serial sections of the hearts of very young animals (dog, cat). The descriptions refer chiefly to the dog.

Constant differences in the affinity of the nerve fibers for the silver are reported. Most of the deeply stained fibers coursing in the cardiac nerves can be traced to the vagus. Pale fibers of various diameters can be followed into the sympathetic ganglia.

which give rami to the heart. They are axones of the sympathetic neurones (sympathetic postganglionics). The preganglionics entering these ganglia stain deeply; the same is true of the preganglionics ending within the intrinsic ganglia of the heart.

In contrast with the sympathetic postganglionics, the axones of the neurones of the ganglia of the cardiac plexus (parasympathetic postganglionics) stain deeply and can be traced to their terminations on the nodes of the conductive system, the arteries and the myocardium of the atria and auricles. The bulk of the parasympathetic postganglionics end on the structures above the coronary sulcus. Few deeply stained fibers are seen in the ventricles, which are supplied chiefly by the sympathetic.

The neurones of the intrinsic cardiac ganglia stain more deeply than those of the sympathetic ganglia.

The ansa subclavia of the dog is described. It conveys afferent fibers of various sizes reaching the middle cervical ganglion in the branches of the middle cardio-sympathetic (accelerator) nerve, issued from this ganglion. None of these fibers seem to enter the cervical sympathetic. Small sympathetic ganglia occur in the ansa.

The cardiosympathetic nerves are then considered; of these the superior, issued from the middle cervical ganglion, does not reach the heart proper but ends on the walls of the large arteries. The middle cardiosympathetic (accelerator) nerve is the largest in the dog, and it supplies chiefly the ventricles. The inferior (cardiac branch of the stellate ganglion), when present, carries afferent fibers from diverse areas of the heart; it may run independently or join the accelerator.

The distribution and composition of the cardiovagal nerve differs on the two sides. The right cardiovagal joins the accelerator of its side soon after emerging from the vagus. It sends numerous preganglionics to the ganglia of the deep cardiac plexus, also fibers to the epithelioid bodies ("paraganglia") between the aorta and the pulmonary artery. The left cardiovagal is an independent nerve which carries the pressoreceptors for the arch of the aorta, base of the left subclavia, and pulmonary bifurcation. It also conveys afferent fibers to the epithelioid bodies and preganglionics to the deep cardiac plexus through a small branch, found in the four puppies examined. Since it receives sympathetic postganglionics from the middle cervical ganglion, it cannot be regarded as a purely vagal branch. Other branches issued from the vagus and recurrent are considered.

The different argyrophilia of the sympathetic and parasympathetic postganglionics, respectively, is discussed. In order to find whether the differences in the impregnation of these axones are correlated with similar differences in the neurofibrils of the cell bodies, the necks of dog fetuses (prepared with the Cajal technique) were examined. This study disclosed well-impregnated neurofibrils in the neurones of the nodose ganglion and in parasympathetic neurones occurring in the glossopharyngeal and in the intercarotid (sinus) nerve, respectively. In the neurones of the superior cervical ganglion the neurofibrillar meshwork does not appear impregnated. It is concluded that the differences observed in very young animals result from conditions present in fetal life.

The existence of free nerve endings in the heart is also considered in view of a recent statement by Stöhr in regard to the presence of a neurofibrillar synectium connecting the vagus and sympathetic fibers. It is pointed out that this "terminal reticulum" has not been found by other investigators using the Bielschowsky method and that such a formation, not always impregnated, consists of argyrophil connective tissue fibers. On the basis of the observations reported in the present article, it is concluded that the vagus component of the heart shows a plexiform, but not a synectial, arrangement and that there are no indications that it merges into meshworks continuous with the sympathetic.



Kapp, Frederic, Friedland, C. K., and Landis, E. M.: The Skin Temperature of Hypertensive Rabbits and the Pressor Effects of Heated Kidney Extracts. *Am. J. Physiol.* 131: 710, 1941.

The cutaneous vessels in the ears of hypertensive rabbits and normal rabbits responded similarly, both quantitatively and qualitatively, to body warming. The hypertensive state induced by renal ischemia was not associated with measurable diminished peripheral blood flow; this indicated another resemblance between experimental hypertension in animals and the hypertensive state in man.

Heated kidney extracts, injected into hypertensive rabbits, raised the blood pressure to extremely high levels without diminishing skin temperature. Apparently the temporary pressor effect of kidney extract is added to the more permanent hypertension due to renal ischemia, without diminishing peripheral blood flow.

When the same kidney extracts were injected into normal and hypertensive rabbits, the rise in blood pressure was slightly greater in the hypertensive group, except that with large doses in markedly hypertensive animals there appeared to be a maximal value of systolic blood pressure which could not be exceeded. Under these circumstances the blood pressure of the hypertensive rabbits was increased by absolute amounts which were less than those observed with the same extract in normal rabbits.

AUTHORS.

Hueper, W. C.: Experimental Studies in Cardiovascular Pathology. III. Polyvinyl Alcohol Atheromatosis in the Arteries of Dogs. *Arch. Path.* 31: 11, 1941.

In dogs repeated intravenous and intraperitoneal injections of a 5 per cent aqueous solution of polyvinyl alcohol result in the development of atheromatous lesions in the aorta and in the carotid and femoral arteries as well as in the appearance of this chemical within the media of smaller arteries and arterioles of the heart and kidney.

The polyvinyl alcohol atheromatosis is morphologically similar to the cholesterol atheromatosis observed in man and rabbits.

The causative mechanism of both types of atheromatosis is represented by a disturbance of the nutritive and oxidative metabolism of the vascular walls brought about by the physicochemical changes prevailing in polyvinylized blood as well as in hyperlipemic conditions.

AUTHOR.

Flexner, James, Bruger, Maurice, and Wright, Irving S.: Experimental Atherosclerosis. II. Effect of Thiamine Hydrochloride and Ascorbic Acid on Experimental Atherosclerosis in Rabbits. *Arch. Path.* 31: 82, 1941.

Thiamine hydrochloride and ascorbic acid neither prevent nor accentuate the rise of the blood cholesterol in rabbits fed cholesterol. Furthermore, these vitamins neither inhibit nor enhance cholesterol-atherosclerosis of the aorta.

AUTHORS.

Katz, Albert: A Contrast Staining Method for Hemosiderin Pigment in Heart Failure Cells. *J. Lab. & Clin. Med.* 26: 700, 1941.

A new staining method here presented allows for a contrast between the heart-failure cells and the surrounding leucocytes. In the sputum, urine, or other material for examination, leucocytes appearing with heart-failure cells are counter-stained by Wright's stain, and the hemosiderin takes a bright green stain. The

hemosiderin pigment stands out in sharply contrasted granules against the well-stained basic blue and acidophilic red of the stained leucocytes and other cells.

AUTHOR.

**Stewart, Harold J.: Mechanism of Diuresis: Alterations in the Specific Gravity of the Blood Plasma With Onset of Diuresis in Heart Failure. J. Clin. Investigation 20: 1, 1941.**

Change in the level of the specific gravity of the plasma has been used as a measure of change in blood volume, decrease in specific gravity indicating dilution of the blood, and increase in specific gravity, concentration. It appeared that diuresis in the presence of heart failure of the congestive type depended on changes initiated in the tissues, since it was accompanied by decrease in specific gravity of the plasma, that is to say, by dilution of the circulating blood with increase in blood volume. Dilution of the blood preceded the onset of diuresis, and increase in blood volume appeared to be the stimulus that initiated diuretic response of the kidneys. The results were similar not only when diuresis occurred spontaneously, but when it was occasioned by digitalis and by theocaine and, moreover, whether in the presence of normal sinus rhythm or of auricular fibrillation, and whether the cause of the heart disease was rheumatic fever, syphilis, arteriosclerosis, or hypertension. These studies do not relate to the anatomic portions of the kidney which take part in the accelerated formation of urine in diuresis.

The specific gravity of the plasma must fall from a high level to 1.0255 or lower for the initiation of diuresis. A value below this level may be said to be in the diuretic zone in heart failure, since it corresponds to a dilution of the blood with increase in blood volume of sufficient magnitude to initiate diuresis.

In uncomplicated heart disease the level of specific gravity of the plasma and, by inference, the plasma proteins is in the normal range not only before the onset of failure but during and after recovery from failure. Plasma protein deficiency does not usually participate in the etiology of cardiac edema.

In the technique of taking blood for determinations of plasma or serum proteins or specific gravity of the plasma, samples should not be obtained when diuresis is being initiated or occurring, since low results which do not reflect the usual level for the subject may be recorded. Results should be interpreted in the light of the effect of diuresis which has been demonstrated in this investigation.

AUTHOR.

**Adams, Wright, and Sandiford, Irene: The Measurement of Cardiac Output. An Improvement of the Acetylene Method Providing an Inherent Check. J. Clin. Investigation 20: 87, 1941.**

In determining arteriovenous oxygen difference with the acetylene method, multiple samples of "alveolar" and "bag" gas make it possible to identify the establishment of lung-bag equilibrium of the acetylene-air mixture and the beginning of recirculation of acetylene-containing blood to the lungs in each instance. Analytical inaccuracies and leaks, as well as most of the many irregularities encountered in a procedure of this type, are identified.

The time required to achieve lung-bag equilibrium and the time of the first appearance of recirculation are variable, but they usually occur much earlier in the period of rebreathing than Grollman indicated.

The interval between the establishment of equilibrium and the occurrence of recirculation varies, but it is usually long enough to allow at least two complete respirations. This is sufficient for an accurate determination of arteriovenous oxygen difference.

Seventy-six per cent of eighty-two determinations were in error by less than 7.5 per cent.

AUTHORS.

Gross, Desiderio: *Oscillometric Studies of the Orthostatic Vasoregulation*. *Rev. argent. de cardiol.* 7: 312, 1940.

Orthostatism induces in normal persons an increase in blood pressure and a reduction of the oscillometric index as measured in the arteries of the lower extremities. In patients with arterial hypertension the increase in blood pressure is also observed but without reduction of the oscillometric index, and in patients with aortic insufficiency there is only moderate reduction of the latter with increase in blood pressure.

The regional increase in blood pressure in the lower extremities and the reduction of the oscillometric index are considered as expressions of regional vasoconstriction induced reflexly by orthostatism as a compensatory mechanism in man. This permanent vasoconstriction may be a determining factor in the pathology of the lower limb arteries.

The great difference in blood pressure between upper and lower extremities which is observed in cases of aortic insufficiency (Hill) is found with equal frequency and intensity in cases of arterial hypertension.

The resistance of the arterial wall has been appreciated indirectly by determinations of mean and diastolic pressure and has been found elevated in cases of hypertension and aortic insufficiency.

The hypothesis is advanced that the increased resistance of the arterial wall, be it due to organic or functional alteration, is the cause of the increased difference of pressure between arms and legs (Hill's sign). The comparison between calculated resistance of the arterial wall and difference between blood pressure measured in arms and that measured in legs lends support to this hypothesis.

AUTHOR.

Waller, John V., Blumgart, Herrman, L., and Volk, Marie C.: *Studies of the Blood in Congestive Heart Failure. With Particular Reference to Reticulocytosis, Erythrocyte Fragility, Bilirubinemia, Urobilinogen Excretion, and Changes in Blood Volume*. *Arch. Int. Med.* 66: 1230, 1940.

In the presence of pronounced manifestations of congestive heart failure with increased venous engorgement and elevated pressure, the plasma volume and total red cell mass are increased, the red cell fragility is increased, and the reticulocyte percentage is elevated. The excretion of urobilinogen in the urine and the serum bilirubin concentration are frequently increased, probably as a result of the impaired liver function resulting from anoxemia. As clinical recovery progresses and the total blood volume decreases, the loss in plasma tends at first to be somewhat greater than the decrease in total red cell mass; this results in a slight temporary elevation of the hematocrit. The excretion of urobilinogen in the stools, although at no time significantly increased above the normal values for ambulatory patients, generally shows higher values during the periods of blood destruction than when the evidences of congestive failure become less marked. During the phase of contracting blood volume the reticulocyte percentage decreases, while the values for red cell fragility, serum bilirubin, and urinary urobilinogen become normal.

AUTHORS.

Knox, J. A. C.: *The Heart Rate During a Simple Exercise*. *Brit. Heart J.* 2: 289, 1940.

A simple two-step cardiac tolerance test of very brief duration is described. The subject's heartbeats are electrically recorded on a smoked drum throughout the test.

The following indices obtained from the analysis of the records of seventy-five healthy male students are discussed: initial rate, maximum rate, time to reach the maximum rate, acceleration of the heart rate, number of extra beats induced by the exercise, actual and percentage increase on initial rate, and the rate after exercise.

The mean values and variability of these indices are given.

AUTHOR.

Cossio, P., and Yopez, C. Gil: Reduplication of the Second Sound in the Clinical Diagnosis of Bundle-Branch Block. *Rev. argent. de cardiol.* 7: 199, 1940.

Heart sounds, electrocardiogram, and venous or arterial pulse were simultaneously recorded in twenty-five patients with bundle-branch block.

Ventricular asynchronism in normal and pathologic conditions is discussed.

The clinical signs of ventricular asynchronism more frequently found were low intensity or reduplication of the first sound, reduplication of the second sound, and, less frequently, a mero-systolic murmur.

Reduplication of the second sound is considered the most significant sign of pathologic asynchronism. Its chief characteristic is a great separation between the two components of the split sound, giving rise to a triple rhythm similar to that observed when an opening snap of the mitral valve or a pericardial snap is present. The triple rhythm due to the latter sounds is heard best over the meso-cardiac area or at the apex, while that due to the reduplicated second sound is heard best over the second intercostal space.

A relation between duration of the QRS complex and ventricular asynchronism is established.

AUTHORS.

Hoff, H. E., Nahum, L. H., and Kisch, Bruno: Influence of Right and Left Ventricles on the Electrocardiogram. *Am. J. Physiol.* 131: 687, 1941.

Extinction of electrical activity of the left ventricle by covering its surface with M/5 KCl permits the recording of the electrogram of the right ventricle, which may be designated as the dextrocardiogram. It is a monophasic-like curve which arises from the R wave and is upright in the three conventional leads.

The levocardigram is similarly obtained by blocking the electrogram of the right ventricle. It is a monophasic-like wave which arises with the S wave and thus is somewhat later in time than the dextrocardiogram. In all conventional leads it is inverted.

The electrocardiogram represents the algebraic sum of the dextro- and levocardigrams.

Similar results were obtained from dogs, cats, and monkeys.

AUTHORS.

Nahum, L. H., Hoff, H. E., and Kisch, Bruno: The Significance of Displacement of the RS-T Segment. *Am. J. Physiol.* 131: 693, 1941.

Elevation of the R-T segment of the electrocardiogram in the dog, cat, and monkey indicates injury to the left ventricle.

Depression of S-T indicates injury to the right ventricle.

When the injury is restricted to a single ventricle, the RS-T interval in all three conventional leads is deflected in the same direction.

Elevation of R-T in one lead and depression of S-T in another indicate that the damage involves contiguous areas of both ventricles.

Elevation in Lead I and depression in Lead III indicate an anterior lesion.

Depression in Lead I and elevation in Lead III indicate an apical or posterior lesion.

Lesions of the anterior surface of the heart are recorded best with the animal on its side, while lesions of the posterior surface of the heart are recorded best with the animal on its back.

AUTHORS.

Hoff, H. E., and Nahum, L. H.: *The Factors Determining the Direction of the T Wave: The Effect of Heat and Cold Upon the Dextro- and Levocardiogram.* Am. J. Physiol. 131: 700, 1941.

The T wave results from the interference of the terminal portions of the dextro- and levocardiograms.

Heat curtails the dextro- and levocardiograms.

Cold prolongs the dextro- or levocardiogram.

Prolongation of the dextrocardiogram or shortening of the levocardiogram causes an upright T wave.

Shortening of the dextrocardiogram or lengthening of the levocardiogram inverts the T wave.

AUTHORS.

Mainzer, F., and Krause, M.: *The Influence of Fear on the Electrocardiogram.* Brit. Heart J. 2: 221, 1940.

On the operating table immediately before induction of general anesthesia, abnormal electrocardiographic records were found to develop in roughly two-fifths of fifty-three cases, in comparison with the tracings of the previous day. These alterations were observed in persons with cardiac disorders, where they merely accentuated the pathologic character of the cardiogram already existing, and also occurred frequently in patients with normal cardiograms. While in a number of patients the changes disappeared during anesthesia, or at least by the next day, they were in some cases still encountered twenty-four hours after the operation.

The changes may be classified into three groups:

A. S-T is depressed below the isoelectric level, and T is low, inverted, or absent altogether, S-T and T showing some deformation similar to that appearing in coronary insufficiency.

B. P and T are high and become sharply pointed, as in neurocirculatory asthenia.

C. A combination of the changes quoted under A and B.

Factors likely to modify the records, other than the excitement owing to fear of the impending operation, can be ruled out. In some patients the curve returns to its original shape even while they are still under the influence of the anesthetic; this supports the hypothesis of a fear reaction.

In view of the analogies existing between "fear-electrocardiograms" and other types of tracings, it is assumed that the curves of type A are brought about by a reduced coronary flow, mainly to be attributed to vagal stimulation; that sympathetic stimulation is responsible for the development of the curves of type B; and that type C is the result of the interaction of both factors. It is improbable that only humoral factors could be active in bringing about these phenomena, in view of their rapid disappearance.

Thus in clinical cardiography a number of abnormal records that can be explained in no other way probably present genuine fear-tracings, particularly where neurotic persons are concerned.

Death from cardiac failure on the operating table immediately before the induction of general anesthesia, as well as during anesthesia, should, therefore, at least in some cases, be considered as the extreme outcome of an otherwise usual fear-reaction.

The coronary spasms of an ordinary attack of angina pectoris may give rise to the formation of microscopically recognizable necrotic foci in the myocardium. Neuro-genic (vagal) lesions of the coronary arteries and myocardium have also been encountered in animal experiments. Thus myocardial damage could be induced by the vasomotor fear-reaction, as becomes apparent in the curves of type A, and could be attributed to coronary constriction of vagal origin.

AUTHORS.

Nyboer, Jan, and Hamilton, James G. M.: Esophageal Electrocardiograms in Auricular Fibrillation. *Brit. Heart J.* 2: 263, 1940.

Nine cases of auricular fibrillation have been examined by means of the esophageal lead; in four a return to normal rhythm was observed.

Auricular intrinsic deflections were obtained in five cases, one of paroxysmal fibrillation, two of recent fibrillation responding to quinidine, and two in which the arrhythmia remained established.

Auricular intrinsic deflections were not found in the remaining four cases, one of paroxysmal and three of established fibrillation.

No association was found between the presence of auricular intrinsic deflections in the esophageal cardiograms of the patients studied and the likelihood of reversion to normal rhythm.

The mechanism of auricular fibrillation is discussed in the light of the curves obtained.

AUTHORS.

Vedoya, R., Videla, Gonzalez, and Aguiar, R.: Sino-Auricular Block. *Rev. argent. de cardiol.* 7: 277, 1940.

The characteristics of the four cases presented confirm the existence of two principal types of sinoauricular block:

Type I: Progressive prolongation of sinoauricular conduction ending in block of one sinus impulse and absence of auricular and ventricular contraction.

Type II: Occasional cardiac standstill, the interval being approximately double the interval between two normal beats. This type is generally known as "sinus arrest."

The delay with which sinus impulses reach the auricles and ventricles favors the escape of secondary centers and may give rise to two situations:

a. The secondary center commands the whole heart perhaps marking the sinus rhythm.

b. The secondary center commands ventricular activity, while the auricles respond to sinus impulses ("dissociation with interference").

The possibility that these may be other forms of sinoauricular block is discussed, e.g., delayed sinoauricular conduction and complete sinoauricular block.

The mechanism of production of this arrhythmia is discussed. Type I cannot be explained by a disturbance in stimuli formation, but suggests an obstacle in the conduction of the impulse from its point of origin to auricular myocardium.

The expression "sinoauricular block" is adequate for all types of the arrhythmia described and should be used instead of the more common "sinus arrest."

AUTHORS.

Geiger, Clyde J., and Hines, Laurence E.: Prenatal Diagnosis of Complete Congenital Heart Block. *J. A. M. A.* 115: 2272, 1941.

A case of complete heart block was diagnosed before birth. A sudden slowing of the fetal heart rate which occurred between seventeen and nineteen hours before birth pointed to the onset of the abnormal mechanism at a specific time. The sudden onset of the heart block demanded a differential diagnosis between heart block and intrauterine asphyxia. No anatomic abnormalities in the heart have been demonstrated, and the child is alive and healthy at 5 months of age.

AUTHORS.

Konstam, Geoffrey, and Sinclair, H. M.: Cardiovascular Disturbances Caused by Deficiency of Vitamin B<sub>1</sub>. *Brit. Heart J.* 2: 231, 1940.

Three cases of cardiovascular disturbances caused by deficiency of vitamin B<sub>1</sub> have been reported in greater London.

In two of them diagnosis was confirmed by finding a very low amount of vitamin B<sub>1</sub> in the blood; in the third no vitamin estimation was done.

Two of the patients were chronic alcoholics, and in one of these cirrhosis of the liver was present. The third lived on a very poor diet with a relatively high carbohydrate content. All three suffered from peripheral neuritis.

Achlorhydria or hypochlorhydria was present in all the cases.

The diagnosis, the reaction to treatment, the influence of diet and alcohol, and other associated factors have been discussed.

AUTHORS.

Swan, W. G. A., and Laws, F.: A Case of Beri-Beri Heart. *Brit. Heart J.* 2: 241, 1940.

A case of beri-beri heart is recorded.

The deficiency was apparently due solely to defective diet.

A clinical cure followed the administration of vitamin B<sub>1</sub>.

Electrocardiographic and radiological changes were present but disappeared after vitamin B<sub>1</sub> had been given to the patient.

AUTHORS.

Warburg, Erik: Myocardial and Pericardial Lesions Due to Non-Penetrating Injury. *Brit. Heart J.* 2: 271, 1940.

Fifty-nine cases of myocardial or pericardial damage due to nonpenetrating blunt injuries have been collected and are reviewed with data from a previous series of 202 similar cases.

The traumatic cardiac lesions described include pericarditis, heart block, myocardial damage, auricular fibrillation and other disturbances of rhythm, and angina pectoris. Auricular fibrillation occurred in one-fifth and angina pectoris in one-fourth of these fifty-nine cases. Seven cases of traumatic coronary thrombosis are cited.

In almost all cases the injury involved the thorax and sometimes the fracture of one or more ribs. However, in a few cases injuries distant from the heart were responsible for cardiac damage.

Arteriosclerosis and hypertension were sometimes present and may have rendered the heart more susceptible to injury from violence to the chest.

AUTHOR.

Wechsler, I. S., and Kaplan, Abraham: Cerebral Abscess (Paradoxical) Accompanying Congenital Heart Disease. *Arch. Int. Med.* 66: 1282, 1940.

The two cases of cerebral abscess are reported, first, because of the rarity of the condition and, second, because early recognition may possibly lead to successful surgical relief. Twelve cases have been reported in the literature, and the two additional ones bring the total to date up to fourteen. In only three, including our own two, was the condition diagnosed during life and therefore treated surgically; in the rest the anomaly was not even suspected. As a rule a diagnosis of embolism or thrombosis is made. The rapidity with which the abscess generally forms justifies in some measure such a diagnosis. But the presence of fever, leucocytosis, possibly slow pulse, and early fundus changes should draw attention to the presence of an expanding intracranial lesion, more particularly an abscess. In cases in which the diagnosis is doubtful, pneumoencephalographic examination may be indicated. The important point to bear in mind is that abscesses of the brain, though rare, can occur in patients with congenital heart disease, even though a primary focus of infection may not be detected. In any event, early recognition as well as familiarity with the complication and with the underlying pathologic changes may lead to more successful surgical intervention.

AUTHORS.

Reindell, H.: Size, Form, and Movement of the Athlete's Heart. *Arch. f. Kreislaufforsch.* 7: 117, 1940.

This monograph covers the historical background and incorporates the author's own x-ray studies of 116 young athletes 15 to 18 years of age and 421 older athletes. He concludes that in youths there is no enlargement of the heart caused by athletics, although the longitudinal diameter increase indicates a left ventricular hypertrophy. In the course of years, enlargement slowly develops with an increase in transverse diameter. The duration and degree of exertion seem to be related to the rate of development of enlargement. Enlargement may be of the left or of the right ventricle. The enlargement of the athlete's heart must be distinguished from that of disease. Kymography may be useful in differentiation. The athlete's heart enlargement is not evidence of heart disease but is a means whereby the greater effort of the athlete may be more readily accomplished.

KATZ.

Christian, Henry A.: The Determinative Background of Subacute Bacterial Endocarditis. *Am. J. M. Sc.* 201: 34, 1941.

If in any disease development takes place frequently on a certain background of pre-existing conditions and if this background is recognized, the probability of the existence of the disease in question is enhanced very greatly. The combination of pre-existing conditions may be called the determinative background of a disease.

The determinative background of subacute bacterial endocarditis is (a) rheumatic heart disease, present in 89.33 per cent of 150 consecutive adult cases of subacute bacterial endocarditis caused by the *Streptococcus viridans*, and in 90.24 per cent of 174 consecutive adult cases of subacute bacterial endocarditis of all causes studied at the Peter Bent Brigham Hospital; (b) absence of auricular fibrillation, noted in 2.66 per cent of the *Streptococcus viridans* cases and in 2.87 per cent of cases of all causes; (c) absence of prior cardiac decompensation, noted in fairly marked degree in only 6.66 per cent of the 150 cases and in severe form in only a few cases; (d) youth, young adults, and male sex (61.33 per cent of the 150 cases).

AUTHOR.



Thomson, Scott, and Innes, James: *Haemolytic Streptococci in the Cardiac Lesions of Acute Rheumatism*. *Brit. M. J.* 2: 733, 1940.

In conclusion, the authors state that, although at the present time the etiology of rheumatic fever cannot be said to be solved, they are inclined to support the view that the cardiac lesions are caused by infection with hemolytic streptococci.

Hemolytic streptococci were isolated from the hearts of five of ten patients dying of acute rheumatism and never from controls.

Hemolytic streptococci were isolated from damaged valves, but not from undamaged valves.

Other types of streptococci were isolated from both damaged and undamaged valves, but more often from the former.

AUTHORS.

Clahr, Jacob, Klein, Milton D., and Greenstein, Nathan M.: *Rheumatic Heart Disease in Pregnant Women*. *New York State J. Med.* 40: 1242, 1940.

The establishment of the prenatal cardiac clinic has led to a threefold increase in the number of diagnosed cases of rheumatic heart disease in pregnancy.

The routine treatment of cases of rheumatic heart disease in pregnancy has been described.

The combination of adequate bed rest and digitalis has been the most effective means in the prevention of intrapartum and post-partum cardiac failure in rheumatic heart disease.

The only maternal deaths occurred in patients who had neither adequate bed rest nor digitalis.

AUTHORS.

Benatt, A., and Taylor, H. J.: *The Vascular Response in Chronic Rheumatoid Arthritis*. *Brit. Heart J.* 2: 281, 1940.

Arthritic changes have been seen in cases in which the blood supply to a joint has been restricted.

Investigations have been carried out to find if there might be any functional vascular disturbance in various types and stages of chronic rheumatoid arthritis. The reaction of rheumatic subjects to contrast baths has been compared with that of normal subjects and of subjects suffering from increased vasoconstrictor tone such as Raynaud's syndrome or acrocyanosis.

Unless a marked postural deformity was present, all rheumatic subjects showed a reaction well within normal limits.

Several types of reaction to contrast baths were obtained in cases of so-called Raynaud's syndrome and acrocyanosis. There was no similarity to the reactions obtained in cases of rheumatoid arthritis.

AUTHORS.

Lewis, Thomas: *A Note on Pulsating Manubrial Tumour*. *Brit. Heart J.* 2: 260, 1940.

Two cases in which pulsating tumors over the upper part of the sternum in syphilitic subjects seemed to indicate pointing aneurysm are briefly described. Both tumors were secondary deposits from hypernephroma, though in one case aneurysmal dilatation of the aorta was also present. The cases are of interest in emphasizing softness and slowness and a slight but just distinct delay in the rise of the pulse in these pulsating neoplasms.

AUTHOR.

Dill, L. V., and Erickson, C. C.: Effect of Constriction of the Renal Arteries in Pregnancy and in Certain Endocrine States of Rabbits. *Arch. Path.* 31: 68, 1941.

Severe renal ischemia in the rabbit produces hypertension, albuminuria, uremia, convulsions, and death. Focal necroses of the myocardium and necroses of the liver occur.

The pregnant rabbit differs from the nonpregnant one in showing increased susceptibility to the effects of renal ischemia or renal injury. The pregnant rabbit demonstrates extensive focal necroses of the liver in a significantly high percentage of experiments.

Renal insufficiency alone or pregnancy alone does not account for the variation of response by the pregnant animal. Other endocrine states do not demonstrate the reaction of the pregnant animal. Hypertension, renal ischemia, or renal injury in association with pregnancy seems to complete the essential combination of factors.

These experimental observations support the thesis suggested in our report of preliminary observations that renal ischemia or renal injury in the pregnant animal produces a syndrome with involvement of physiologic factors similar to, and production of pathologic lesions analogous to, those in at least some of the human toxemias of pregnancy.

AUTHORS.

Nesbit, Reed M., and Ratliff, Rigdon K.: Hypertension Associated With Unilateral Renal Disease. *J. A. M. A.* 116: 194, 1941.

Experimental evidence and clinical observations have shown that hypertension may result from pathologic conditions of the kidney which may be bilateral or unilateral.

Three different types of unilateral renal lesions are most commonly associated with hypertension: (1) those produced by gross vascular occlusion of the renal arteries including trauma to the kidney, (2) the obstructive uropathies, and (3) chronic inflammatory lesions.

Since chronic infection appears to be the most important etiologic factor, it would appear that the best treatment of this type is prophylactic. In this regard the value of modern chemotherapeutic methods for the prevention of chronic infections of the urinary tract cannot be overemphasized.

Hypertensive patients should be submitted to complete urologic study as a part of the routine examination, even in the absence of a history of renal disorders or urinary findings suggesting disease of the urinary tract.

The rational treatment of the hypertensive patient with unilateral nephropathy is removal of the diseased kidney, provided the function of the opposite kidney is not significantly reduced. With this restriction, a reasonable expectancy of improvement or cure can be hoped for in the majority of cases.

NAIDE.

Howard, T. L., Forbes, R. P., and Lipscomb, W. R.: Aneurysm of the Left Renal Artery in a Child 5 Years Old With Persistent Hypertension. *J. Urol.* 44: 808, 1940.

A case of persistent hypertension as a result of a multilocular aneurysm of the left renal artery in a 5-year-old child is reported. The hypertension was relieved by nephrectomy.

NAIDE.

Sprague, P. H.: A Case of Temporal Arteritis (Horton-Magath Syndrome). *Canad. M. A. J.* 43: 562, 1940.

A case of arteritis of the temporal arteries is reported. This entity was first described by Horton, Magath, and Brown. The condition, in the patient reported, simulated temporal neuralgia and temporomandibular arthralgia before the correct diagnosis was made. The clinical features of the syndrome are its incidence in the fifth and sixth decades, the prolonged febrile course, loss of weight, anemia, anorexia, and weakness. It must be differentiated from periarteritis nodosa, thromboangiitis obliterans, and rheumatic arteritis. The arteritis is probably not limited to the temporal arteries but may involve other arteries as well.

NAIDE.

Mathe, Charles Pierre: Thromboangiitis Obliterans (Buerger's Disease) of the Spermatic Arteries: Report of a Case. *J. Urol.* 44: 768, 1940.

A case of thromboangiitis obliterans of the spermatic arteries which was treated by orchidectomy is reported in detail.

Pathologic examination revealed thrombosis of the spermatic arteries and anemic infarct of the central segment of the testis. The pathologic changes encountered in the walls of the spermatic vessels and in the perivascular tissues, as well as the nature of the thrombus, were characteristic of Buerger's disease.

NAIDE.

Griffiths, D. L.: Volkmann's Ischemic Contracture. *Brit. J. Surg.* 28: 239, 1940.

Observations upon thirty-two cases support the theory that Volkmann's ischemic contracture is due to arterial injury and to the accompanying spasm of the collateral circulation. Clinical signs of arterial occlusion in acute and chronic cases occur regularly, and the histology is shown to be that of muscle infarction. The idea that the contracture results from venous occlusion is rejected because of the absence of any venous compression by hematoma in acute cases, the discovery of arterial lesions in operations at all stages, the occurrence of the contracture after arterial embolectomy, and the production of the lesion in a small series of rabbits by arterial ligation.

The early diagnosis of the lesion is discussed, and its prevention by operations designed to relieve arterial obstruction and collateral spasm is described. Preventive treatment must be initiated early, since the fate of the infarcted muscle is decided by hours and not days. Any case showing absence or weakness of radial pulse following a limb fracture is in danger of developing the Volkmann syndrome.

NAIDE.

Edwards, Edward A., Hamilton, James B., Duntley, S. Quimby, and Hubert, Gilbert: Cutaneous Vascular and Pigmentary Changes in Castrate and Eunuchoid Men. *Endocrinology* 28: 119, 1941.

With the aid of the Hardy recording spectrophotometer, studies of the cutaneous vascularity and pigmentation of four human male castrates and five eunuchoid patients were carried out before, during, and after treatment with testosterone propionate. In the castrates there was a generally diminished quantity of hemoglobin in the skin, with a higher than normal proportion in the reduced state. This is interpreted as an indication of a smaller cutaneous vascular bed than normal with less blood flow through the region. Administration of testosterone propionate reversed these changes.

Carotene was present in excessive quantity in the skin of untreated castrates but was reduced to normal levels by administration of testosterone propionate. The eunuchoids showed less deviation from normal than the castrates.

SCHWARTZ.

Dickens, Karl L.: Pulmonary Stenosis Produced by Aneurysm of the Ascending Aorta. *Brit. Heart J.* 2: 247, 1940.

A case is reported in which an aneurysm of the aorta was so located as to produce pulmonary stenosis and insufficiency and a clinical picture suggestive of aneurysm of the pulmonary artery. Previous reports are briefly reviewed, and it is pointed out that the location of the aneurysm in the reported case is very unusual, as are its ultimate effects upon the pulmonary system.

AUTHOR.

Loeffler, Louis: Pulmonary Embolism and Infarction. *Arch. Path.* 31: 93, 1941.

In guinea pigs and rats a string tied moderately tightly around a lobe of the lung produced hemorrhagic infarction. The tying of a string suddenly and tightly around a lobe produced anemic necrosis.

Stoppage of the blood supply to the kidneys, liver, lungs, and intestines, to summarize the present and previous experiments, produced anemic necrosis, an observation that might be applied to any organ.

A hemorrhagic infarct, wherever it occurs, requires a continuous blood current and increased venous pressure. The continuous blood flow is maintained either by collaterals, as in the lungs, or by incomplete occlusion of the arteries, as in the intestines.

Occlusion of the pulmonary artery at any point of its course does not, as a rule, cause serious disturbance of the lung tissue, because there is sufficient collateral circulation through the bronchial arteries. The anemic and the hemorrhagic infarcts in lungs represent exceptions to this rule, due to special conditions.

AUTHOR.

Mason, David G.: Subacute Cor Pulmonale. *Arch. Int. Med.* 66: 1221, 1940.

An example of a case of subacute cor pulmonale is presented. Death was caused by fairly rapid obstruction (clinically recognized twenty-seven days) of the pulmonary arterioles and pre-arteriolar arteries, with ensuing failure of the right side of the heart. The vascular obstruction was due to emboli of small carcinoma cells arising from a primary carcinoma of the breast, for which radical mastectomy had been performed nineteen months previously.

AUTHOR.

Wilkinson, K. D.: Aneurysmal Dilatation of the Pulmonary Artery. *Brit. Heart J.* 2: 255, 1941.

A case is reported in which an aneurysmal dilatation of the pulmonary artery, due to a congenital defect, led to sudden death from rupture of the walls of the artery, the rupture also producing some degree of dissection of the coats of the artery.

AUTHOR.

Heller, Richard E.: The Pathological Physiology of Varicose Veins. *Surg. Gynec. & Obst.* 71: 566, 1940.

This is an excellent review of the normal venous circulation and the physiology of varicose veins.

NAIDE.

Dougherty, John, and Homans, John: *Venography, a Clinical Study.* Surg. Gynec. & Obst. 71: 697, 1940.

An experimental study in venography is presented in which fifteen cases, six normal and nine abnormal, were studied. The study was limited to the lower extremities and the adjacent portions of the body and was principally concerned with thrombosis.

A 50 per cent solution of an organic iodide commercially known as diodrast (compound) was used in conjunction with an infusion set-up containing physiologic saline solution. In none of the cases was there evidence of reaction.

Two cases are illustrated by photographs of the venograms. The first was a case of acute femoro-iliac thrombophlebitis accompanied by arterial spasm. The second was a case of traumatic femoro-iliac thrombosis, subsequently canalized and complicated by recurrent small embolisms. For comparison, a normal venogram is presented. The literature, both foreign and local, is very briefly reviewed.

NAIDE.

Keen, J. A.: *A Case of Complete Obstruction of the Inferior Vena Cava.* Brit. M. J. 2: 823, 1940.

Complete obstruction of the inferior vena cava was discovered accidentally in a dissecting-room subject, a colored man, aged 71 years. There was nothing in the clinical history which gave any explanation of the causation of the venous thrombosis. The man was blind and spent the last eleven years of his life at the Capetown Infirmary. He was not bedridden and could get about for walks. His last illness was a rather sudden collapse with pulmonary congestion; nothing abnormal was found in the abdomen or urine during the last few days before his death.

A short account is given of the anatomy of a case that demonstrates the remarkable potentialities of the body for establishing circulatory anastomoses.

From this case it appears to be possible to establish a complete collateral circulation for the drainage of both kidneys.

AUTHOR.

Heggin, R.: *The Circulation in Disturbed Sugar Metabolism, Especially in Diabetic Coma.* Arch. f. Kreislaufforsch. 7: 1, 1940.

In ten cases of diabetic coma, the occurrence of an S-T depression in Leads I and II and flattening of T in these leads was found, as well as lengthening of electrical systole. Insulin therapy exaggerated these changes. Mechanical systole, measured from heart sound records, was abbreviated in diabetic coma.

KATZ.

Bowers, Warner F., and Kennedy, John C.: *Improved Management of Gangrene of the Foot.* Am. J. Surg. 50: 573, 1940.

The authors advise débridement as a preliminary to major amputation in patients with arteriosclerotic gangrene with a septic type of temperature curve. A major amputation is performed after the temperature has been down for two days.

NAIDE.

## Book Reviews

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**THE PHARMACOLOGICAL BASIS OF THERAPEUTICS:** By Louis Goodman, M.D., Assistant Professor of Pharmacology and Toxicology, Yale University School of Medicine, and Alfred Gilman, Ph.D., Assistant Professor of Pharmacology and Toxicology, Yale University School of Medicine. 1941, The Macmillan Company, New York, 1383 pages, 126 figures. \$12.50.

This book differs from other manuals of pharmacology in that the action of drugs on healthy persons and on the sick is treated far more extensively. It is the best compilation available concerning the action of drugs, as judged by observations made on man.

ISAAC STARR.

**THE ELECTROCARDIOGRAM AND X-RAY CONFIGURATION OF THE HEART:** By Arthur M. Master, M.D., Associate in Medicine and Chief of the Cardiographic Laboratory, Mt. Sinai Hospital, New York; Associate in Medicine, College of Physicians and Surgeons, Columbia University. Lea and Febiger, Philadelphia, 1939, 222 pages, 71 illustrations, \$6.50.

This monograph presents a correlation between roentgenographic and electrocardiographic observations, first, on the normal heart, with particular reference to age, position of the body, habitus, obesity, and pregnancy, and, second, on heart disease caused by hypertension, valvular lesions, congenital malformations, pericarditis, metabolic disturbances, pulmonary disease, and deformities of the chest. The material is presented in atlas form; the roentgenograms and electrocardiograms are side by side, with ample text and legends. As far as a correlation between the two methods is possible, it has been brought out in a very useful and good didactic manner. One is grateful that the author, as a real clinician, presents the clinical background in each case. This may help to combat the unfortunate tendency to render diagnostic service by excessive specialization, such as "reading" electrocardiograms or roentgenograms. The material should be quite valuable, particularly for the beginner.

It is only natural that reviewers should not always be in full agreement with authors, and, in submitting this criticism, it is hoped that some of it will seem acceptable to the author, and perhaps be incorporated in a second edition. In order to give readers of the monograph an opportunity to form their own opinions, it seemed wise to refer specifically to each instance in which a divergent opinion is held.

With respect to the electrocardiograms.—Fig. 21 illustrates right axis deviation as it occurs with the vertical type of heart. It may simulate that of mitral valve disease, but there is not much danger of confusing them because the electrocardiogram which is shown reveals a predominance of  $P_2$  and  $P_3$ , whereas with mitral disease, if stenosis prevails, predominance of  $P_1$  and  $P_2$  is observed as a rule. This, for instance, is demonstrated in Fig. 42. Figs. 28 and 44 are accompanied by a statement that a small initial positive deflection in the chest lead (leading from the precordium just within the apex, and from the left leg) is frequently seen when the heart is large. This is noted, of course, when the exploring electrode is placed over the right ventricle; the intrinsic deflection would be high, or higher; if the electrode were placed further to the left, and the lesson is that taking one chest

lead only may give insufficient information. Fig. 28, as well as others, depicts the electrocardiogram which is typical of hypertension, and reference is made to the normal duration of the QRS complex. To point out that, with high voltage, the area of the QRS complex is increased, and that this factor influences the direction of the T deflection, might have been useful. Fig. 30 is said to show a deep  $Q_1$ , which is interpreted as indicating involvement of the myocardium; this wave is really  $S_1$ . The same wave, which is supposed to be indicative of myocardial damage in Fig. 30, is interpreted in Fig. 28 as evidence of cardiac enlargement. Fig. 34 is said to illustrate marked left axis deviation and high voltage of QRS as a result of ventricular enlargement. The correct interpretation is that a relatively low  $R_1$ , when it is associated with a deep  $S_1$  and  $S_2$ , is indicative of anterior infarction, usually with aneurysm of the heart, which the author properly presents as such. The legend of Fig. 35 states that slight left axis deviation indicates slight left ventricular enlargement. This is certainly unacceptable. In connection with Fig. 39 there is no mention of prolongation of the Q-T segment. This case, by the way, demonstrates nicely that high voltage, with left axis deviation and normal T deflections in Leads I, II, and IV, may be associated with a marked degree of left ventricular enlargement, caused, in this instance, by aortic regurgitation of syphilitic origin. Fig. 40, from a patient with aneurysm of the aorta and no cardiac enlargement, is accompanied by the statement that the electrocardiogram is entirely normal because the size, shape, and position of the heart are normal. Another reason, however, might be that there was no encroachment on the coronary ostia. In several illustrations, inversion of  $T_2$  and  $T_3$  is interpreted as evidence of right ventricular enlargement. In the case of Fig. 44, however, it is quite certain that this was caused by digitalis, judging from the concavity of S-T in Lead I and the maximal depression of S-T in Lead II. Figs. 45, 54, and 56 reveal a high  $R_2$  with right axis deviation. In connection with Figs. 45 and 54, the author says that high voltage of QRS is associated with enlargement of the left ventricle, but, as a matter of fact, it is also noted with right ventricular enlargement. Obviously, difficulties will arise with respect to both Figs. 54 and 56; left ventricular hypertrophy is out of the question in these cases because of the type of congenital malformation which was present. In connection with Fig. 56, the author speaks of high voltage of QRS in association with an increase in the muscle mass of the heart. Fig. 46 is said to show widening of the P waves, but this is not apparent. The description of Fig. 57 states that its slurred and abnormally long QRS complexes indicate myocardial disease, but this record really shows left bundle branch block. Fig. 58 depicts the electrocardiogram in a case of dextrocardia. The illustration is not well chosen, first, because the voltage of QRS in Lead II is larger than in Lead III, and the reverse holds true for the electrocardiogram in dextrocardia as a part of complete inversion, and, second, because of the diphasic character of QRS. The latter is indicative of an associated congenital anomaly, the existence of which, by the way, is further evidenced by the cardiac enlargement shown in the roentgenogram. Fig. 59 shows high P deflections after recent cardiac infarction, and it is pointed out that the P deflections returned to normal within several weeks. This is correct, but it is also interesting to note that simultaneously the voltage of QRS diminished greatly. Fig. 62 shows a negative  $P_2$  and  $P_3$  in a case of chronic bronchitis and emphysema, and this is regarded as evidence of displacement and rotation of the heart. The accompanying roentgenogram does not reveal displacement, and if the cardiac rotation was the result of low position of the diaphragm, why should P become negative in Leads II and III? The direction of the P deflection, in conjunction with a P-R interval of 0.11 second, makes this an obvious case of nodal rhythm. It would have been more instructive to present a case in which  $P_2$  and  $P_3$  were high; this is common, although not constant, with chronic "cor pulmonale."

With respect to the roentgenograms.—Two basic premises are not fulfilled. First, with very few exceptions, only anterior views are presented, and this limits one's ability to detect cardiac enlargement, especially enlargement of individual chambers. Right ventricular enlargement may thus escape notice; and this explains, for instance, why the author on page 183 states that in uncomplicated emphysema the heart is usually of normal size, although on page 182 he cites the excellent and correct observations of Parkinson and Hoyle, who came to opposite conclusions. Second, it is stated that the roentgenograms were taken at the end of moderate inspiration. As a matter of fact, many of them show that they were made during deep inspiration. This is unfortunate because inspiration causes an unphysiologic position, and hence a morphologically distorted roentgenographic appearance of the cardiovascular silhouette is obtained; also, the roentgenograms are correlated with electrocardiograms which, as a rule, are not taken during deep inspiration. Figs. 1 and 4 are supposed to show normal positions, but actually this is not the case; the narrow shape in Fig. 22 is exaggerated, and Fig. 32 seems to show that the size of the heart is normal (case of long-standing hypertension). Fig. 21 is supposed to illustrate a long, narrow heart, with rotation of the right ventricle forward, but the right ventricle cannot come to lie farther forward than it naturally does. Figs. 7, 8, 23, and 24 are supposed to reveal left ventricular enlargement, but this is not apparent. The roentgenogram shown in Fig. 35 is said to be typical of aortic insufficiency. Such a diagnosis could hardly be made without studying the pulsations fluoroscopically. Page 118 carries the statement that aortic stenosis produces left ventricular enlargement; this is not necessarily true, for hypertrophy, per se, need not cause appreciable enlargement. Fig. 46 shows the cardiac shadow reaching the right side of the costal cage, and this is ascribed to huge enlargement of the right auricle. Actually, it is caused by so-called aneurysmal dilatation of the left atrium. On page 153 it is stated that patency of the foramen ovale brings about enlargement of the auricles. This is not the case. Fig. 54 is said to show that a sharp convexity of the right border of the heart indicates enlargement of the right ventricle. As a matter of fact, right ventricular enlargement does not produce such a contour.

Finally, a few suggestions are submitted with respect to nomenclature, namely, roentgenogram instead of x-ray film, extrapericardial fat instead of pericardial fat, conus of the right ventricle instead of pulmonary conus, atrium instead of auricle (unless used in connection with the term appendage), postural circulatory deficiency instead of neurocirculatory asthenia syndrome. The terms cardiac infarction and coronary occlusion appear to have been used somewhat promiscuously.

HUGO ROESLER.

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#### Books Received

LA INSUFICIENCIA CARDIACA: By Dr. Cristián Cortés Lladó, Antiguo Jefe del Servicio de Cardiología de Cataluña. De la Escuela de Medicina de Barcelona. Compañía General Editora, S. A., Mexico, D. F., 1940, 186 pages, 30 illustrations.

THE VASOMOTOR SYSTEM IN ANOXIA AND ASPHYXIA: By Ernst Gellhorn, M.D., Ph.D., Professor of Physiology, University of Illinois, and Edward H. Lambert, M.D. University of Illinois Press, Urbana, Ill., 1939, 71 pages, 21 illustrations, \$1.50.



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\**Executive Committee.*

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## Original Communications

### CORONARY EMBOLISM\*

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MANY years ago, when I came to New York to begin my internship in medicine at the New York Hospital, Dr. Conner was in charge of the medical service at the Hudson Street Annex. He came often to the old hospital on Fifteenth Street to see interesting cases, and on occasions substituted at ward rounds for the regular attending physician. He was pointed out to me by my associates as the most promising of the young men in New York devoting themselves to internal medicine. It was not difficult for me to accept this high estimate of his character and ability. His comely figure, his courteous and gracious, yet dignified and reserved, manner, his professional ability and untiring zeal set him apart as unusually gifted and determined to make the most of his gifts. Too often does the flame of promise, burning brightly in youth, subside after a few years to a flickering glow that is soon extinguished. Happily, not so in Doctor Conner. With the passing years the early presage of a distinguished career has been increasingly fulfilled, so that now, in the autumn of his life, he has grown to the stature of a great and inspiring physician. The gods seem to have showered upon him all their gifts. Not only has he preserved the figure and physical energy of youth but as well its mental vigor and indefatigable interest. I have never had the good fortune to be intimately associated with Doctor Conner, but I have seen him often during the intervening years and my admiration and affection steadily have grown.

This being my regard for him you will readily understand what great pleasure I derived from your invitation and that I esteem it a high honor to have been asked to give this lecture.

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When we speak of coronary occlusion we have in mind chiefly coronary thrombosis. Indeed in conversation, and sometimes in medical writings, the terms are used as though they were synonymous. As a matter of fact there is some excuse for this identification since, whatever may be

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the cause of the occlusion, in the end thrombosis nearly always occurs, and thrombosis developing as an independent and primary condition, in the absence of any disease of the arterial wall or its lumen, due solely to some disorder of the blood, is a great rarity. However, as a rule the term thrombosis is not used in this all-inclusive sense, nor is it so understood, but in the more restricted sense of accompanying or following arteriosclerotic disease of the coronary arteries. For instance, were a physician to speak simply of coronary thrombosis I think we would be surprised to learn that he had meant to include under this heading the compression of an artery from without, or inflammation of the wall of an artery as occurs in periarteritis nodosa, or thrombosis following rupture of the artery, or embolic occlusion of an artery, or the gradual sealing of the mouth of a coronary artery by the encroachment of syphilitic disease of the aorta. It is an established custom that when we speak of these uncommon causes of coronary occlusion we are to mention them specifically.

The symptoms and the pathologic anatomy of coronary occlusion have been diligently investigated during the past fifteen years so that at present everyone is familiar with the important clinical facts and their underlying causes. Nevertheless I have no doubt that information of value is still to be got from a detailed study of some of the less common features of the condition. The predominant cause of coronary occlusion is arteriosclerosis, and it predominates to such a degree that we are apt to neglect or forget other occasional causes. I have selected coronary embolism as the topic of my remarks not to excite your curiosity with the details of an idle search for the recondite, but because I believe there is something to be said about it of a little practical importance.

When we consider coronary embolism with our attention focused upon its clinical manifestations, it is desirable to separate the subject into two divisions, embolic occlusion of large coronary branches which are usually single, and embolic occlusion of small coronary branches which are nearly always multiple. This division is desirable because the symptoms of the two conditions are entirely different; therefore, it would be confusing to consider them together. When clinicians speak of coronary embolism, they always have in mind the occlusion of large vessels. Indeed the embolic occlusion of many small branches of the coronary arteries, although it is a condition well known to the pathologist, has not been deemed of sufficient clinical importance to merit more than passing notice.

#### I. EMBOLIC OCCLUSION OF LARGE BRANCHES OF THE CORONARY ARTERIES

Saphir, in 1932, collected from the literature sixteen cases of coronary embolism and added to these three cases he had observed himself. Without pretending to have made a thorough search I have found eleven cases reported since the publication of Saphir's article. In the index of the

pathologic records of the Johns Hopkins Hospital the diagnosis of coronary embolism appears for the first time in 1931. During the nine succeeding years, from 1931 to 1939, the diagnosis has been entered ten times. An analysis of these forty cases will furnish the substance of my remarks.

I would not have you believe that only forty instances of coronary embolism have occurred since the first observation briefly reported by Virchow in 1856. The condition would be very rare indeed were this inference tenable. On the contrary there are many valid reasons for concluding that coronary embolism is much more frequent than these figures indicate. It is only reasonable to assume that but a small number of the cases encountered at autopsy have been reported. As I shall have occasion to point out later, the most frequent source of coronary emboli is bacterial vegetations upon the heart valves. This association is so frequently observed as to be almost a commonplace, and it would be trite to report these cases unless the circumstances of a particular instance were unusual or else as part of a statistical study. At present we can form no accurate estimate of the true incidence of coronary embolism although the results of a number of statistical studies allow an approximation. For instance Levy, Bruenn, and Kurtz found six instances of embolism in a study of the pathologic records of 762 cases of coronary occlusion; Appelbaum and Nicolson four cases of embolism, all due to bacterial vegetations, among 168 cases; Kirschbaum four instances of embolism, all associated with bacterial endocarditis, among 612 cases of severe disease of the coronary arteries. Moreover it is likely that many instances of embolism have been misinterpreted at the post-mortem examination. As a rule it is difficult to establish the diagnosis of coronary embolism, and only rarely would the diagnosis be made unless the possibility of its occurrence were kept in mind and the evidence carefully sought for. The fact that the diagnosis of coronary embolism was registered for the first time at the Johns Hopkins Hospital in 1931 and ten times in the succeeding nine years invites comment. Shall we conclude that the condition had not occurred during the more than fifty years before 1931 and then suddenly had occurred ten times during the following nine years? This is improbable to the last degree. It is certainly true that we see what we look for, and this adage no doubt explains the sudden occurrence and the sustained incidence of coronary embolism. I think we may conservatively estimate that from 1 to 2 per cent of the cases of coronary occlusion are due to embolism, and I predict that the proportion will rise as interest and familiarity incite more thorough investigation.

There are six possible sources for emboli which may occlude the coronary arteries: (1) A thrombus or atheromatous material in a coronary artery; (2) a thrombus covering an arteriosclerotic plaque at the root of the aorta; (3) bacterial vegetations upon the mitral or aortic valves; (4) intracardiac mural thrombi; (5) thrombi in the pulmonary veins; (6)

thrombi in the peripheral veins, paradoxical embolism. Instances of coronary embolism from all six of these sources have been reported. In the forty collected cases the source of the embolus is not stated in two. In the remaining thirty-eight cases two belong in the first group, six in the second, nineteen in the third, five in the fourth, two in the fifth, and four in the sixth.

1. *Emboli coming from a thrombus or atheromatous material in a coronary artery*

This form of coronary embolism has little clinical interest. Since it follows disease of the coronary arteries in most instances it will add nothing to the symptoms already present, or at most unimportant details. Occasionally calcareous deposits on an atheromatous ulcer in a large coronary artery may become detached without a thrombus being formed at that location, and these free deposits, propelled by the blood stream, may lodge at the first point of bifurcation they meet, producing occlusion at this point. Or, a thrombus on a sclerotic patch which does not completely obstruct the lumen may become loosened and occlude a smaller branch further on. Under these circumstances literally the coronary occlusion is the result of embolism but the embolus is incidental to already existing coronary disease. This is a different matter from an embolus entering the coronary circulation from without. Whatever interest may be attached to it concerns the pathologist more than it does the clinician. Nevertheless for the sake of completeness I will notice briefly the two cases which have been reported.

Huber, in 1882, reported the case of a man of 64 years who had died suddenly. At autopsy an embolus was found occluding the descending branch of the left coronary artery. The embolus had come from a thrombus in the main stem of the left coronary artery.

Saphir describes the heart of a man of 70 years who entered the hospital with typical attacks of angina pectoris. The heart was enlarged, the sounds feeble, and a pericardial friction was heard. There were the usual signs of a moderate degree of chronic passive congestion. A few days after admission auricular fibrillation came on. Under treatment the patient improved somewhat but on the sixth hospital day he died suddenly. The post-mortem examination disclosed diffuse arteriosclerosis and advanced sclerosis of the coronary arteries. The heart was hypertrophied and dilated. There was recent infarction of the lateroposterior wall of the left ventricle. There was an acute fibrinous pericarditis. In the circumflex branch of the right coronary artery, at a point about 1 cm. from its mouth, there was an atheromatous ulcer with a small thrombus over it; at the point where the posterior descending branch comes off from the circumflex artery, there was an embolus about 1 cm. in length which completely occluded the lumen of the right branch of the circumflex artery.

2. *Coronary emboli coming from thrombi located upon arteriosclerotic plaques at the root of the aorta*

I was surprised to find six instances of this condition among the thirty-eight collected cases. In point of incidence it is second only to bacterial endocarditis.

The first case was reported by Heektoen in 1892. A man, 32 years of age, died suddenly. An embolus was found in the left coronary artery at the site of division into the descending and circumflex branches. The embolus had come from a parietal thrombus in the aorta.

Oestreich reports the case of a man, 30 years of age, who died suddenly on the night of his wedding. There was an arteriosclerotic ulcer covered by a thrombus at the root of the aorta. The mural thrombus had occluded the mouth of the right coronary artery. There was an embolus in the main stem of the left coronary artery.

Chiari performed the autopsy upon a man of 32 who had died suddenly. There was embolic occlusion of the main stem of the left coronary artery and an organizing thrombus occluding the mouth of the right coronary. The source of the embolus was a thrombus covering a small atheromatous ulcer in the aorta.

Kauffman's case was that of a man, 35 years of age, who had died suddenly. An embolus was found in the descending branch of the left coronary artery which had come from a thrombus on the aortic wall just above the posterior cusp of the aortic valve.

The patient reported by Saphir was a man, 72 years of age, who had had attacks of angina pectoris for 17 years. A little over a year before he died he had had an attack diagnosed coronary thrombosis. He recovered and was well for a year, when he had a second severe attack, followed by the symptoms of myocardial insufficiency. Under treatment he improved but died suddenly three weeks after the onset of the attack. The heart was enlarged. At the left apex there was an aneurysm. The myocardium was diffusely fibrotic. There was pronounced sclerosis of the coronary arteries and an old completely organized thrombus occluding the descending branch of the left coronary artery. The mouth of the right coronary artery was plugged by a recent embolus which, to all appearances, had come from a thrombus covering an atheromatous ulcer in the wall of the aorta just below the mouth of the artery.

The patient observed at the Johns Hopkins Hospital (Autopsy No. 15091) was a colored man about 24 years of age. He was dead when he arrived at the hospital. The heart was not enlarged and was grossly normal in appearance, but under the microscope there were many small scars in the right ventricle. The intima of the aorta was superficially roughened at a point a little above the orifice of the left coronary artery. Over this area of roughness there was a thrombus, the lower end of which projected into the mouth of the artery for the distance of a centimeter. There was another embolus in the right coronary artery, apparently a little older than the one in the left, since at one point there was beginning organization of the thrombus. Microscopic examination of the aorta demonstrated the characteristic changes of early syphilitic disease.

The six cases in this group were all men and five of them were relatively young, from 24 to 35 years of age. In four of these five the disease of the aorta upon which the thrombus formed was arteriosclerosis, in one it was syphilis. Only in the man of 72 years of age was there extensive sclerosis of the aorta; in the four other instances of arteriosclerosis, affecting younger men, the disease was localized. Plaques of arteriosclerosis in the aorta are not uncommon in persons from 30 to 40 years of age, and it is interesting to observe that occasionally coronary embolism may be the first and only symptom due to their presence.

### 3. *Coronary emboli coming from vegetations upon the heart valves*

The commonest source of coronary emboli is bacterial endocarditis. In the thirty-eight cases I have assembled, eighteen, or 50 per cent, be-

long to this group. Of the ten cases recorded at the Johns Hopkins Hospital, in six the embolus consisted of fragments of bacterial vegetations. Sometimes filamentous outgrowths of vegetations from the aortic valves wave about in the blood stream and may be floated into the mouth of a coronary artery; more often fragments of vegetations break off and are carried by a favoring current into the coronary circulation. These emboli, when big enough to plug large coronary vessels, are a not uncommon cause of sudden death in bacterial endocarditis. As I have said, these observations are matters of common knowledge and nothing further need be said about them.

#### 4. *Coronary emboli coming from mural thrombi within the heart*

Dr. Garvin, the preceding speaker, has called our attention to the frequency with which mural thrombi occur in heart disease. In a consecutive series of 771 adults dying of heart disease, mural thrombi were found in 265, or over 34 per cent. Mural thrombi were found in the left side of the heart in 193 of the cases. I need only refer to what is already well known, namely, that the presence of these mural thrombi punctuates the course of heart disease with interesting and often dramatic symptoms. In the present relation, using Dr. Garvin's figures, I wish only to recall to your minds that in 25 per cent of all cases of heart disease there are mural thrombi in the left side of the heart, a condition threatening the occurrence of coronary embolism. These mural thrombi are friable, and small bits frequently break off and float free in the blood stream. These small emboli cause no symptoms or at most inconspicuous symptoms which we cannot ascribe confidently to embolism. Sometimes careful post-mortem examination will demonstrate to our surprise that they have occurred in great profusion, when clinically we have been unable to detect their presence. Less often, but still not infrequently, larger bits of the thrombus break off. However, even these usually pass unnoticed since most of them occlude arteries which are not end arteries or produce small infarcts in organs which give no signs of the loss of a small amount of tissue. Only when they are large enough to occlude big arteries or lodge in organs in which even relatively small infarcts produce grave symptoms do we become aware of their presence. The two organs most sensitive to infarction are the brain and the heart.

In heart disease evidence of cerebral embolism occurs commonly, of coronary embolism, infrequently. When we consider the size and position of the coronary arteries and the peculiarities of the coronary circulation, this relative incidence is not remarkable.

Among the thirty-eight assembled cases of coronary embolism, in five the embolus came from mural cardiac thrombi.

Rolleston in 1896 reported the case of a man, 17 years of age, who died suddenly. At autopsy an embolus was found in the descending branch of the left coronary artery. In the left ventricle there was a mural thrombus.

The patient of Gallaverdin and Dufourt was a man, 63 years of age, who died suddenly. The post-mortem examination revealed an embolus in the descending branch of the left coronary artery. There was an old myocardial scar with a mural thrombus.

Hadorn reports the case of a bicycle racer, 39 years of age, taken suddenly with severe pain in the left shoulder and arm, followed by severe vomiting. The pain persisted and later was located also beneath the sternum and over the upper portion of the abdomen. There were fever, shortness of breath and cough. Six days after onset he was admitted to the hospital with a diagnosis of pneumonia. The heart was enlarged, the sounds loud; there was a systolic murmur and the second pulmonary sound was accentuated. The patient was prostrated and short of breath. There were the usual signs of congestive failure. A pleural effusion on the right was tapped, and the fluid had the characteristic features of a transudate. The electrocardiogram was typical of anterior infarction. The patient improved somewhat but died suddenly fourteen days after the onset of the attack of pain. At autopsy the heart was found to be enlarged. There was a sero-fibrinous pericarditis. In the anterior portion of the left ventricle there was an infarct, at the apex an aneurysm, and mural thrombi in both ventricles. There was pronounced sclerosis of the coronary arteries. In the descending branch of the left coronary artery there was an old organizing thrombus; above this, plugging the mouth of the artery, there was a fresh embolus.

Two of the cases from the records of the Johns Hopkins Hospital fall into this group.

A colored man, 50 years of age, entered the hospital April 12, 1939 (History No. 138265), complaining of shortness of breath and palpitation of the heart. The symptoms had appeared two years before and had steadily become more and more pronounced. Four months before admission he had developed severe attacks of coughing accompanied by urgent dyspnea, and on one occasion the sputum had been bloody. These symptoms had gradually abated. Two days before admission he had been seized with severe pain in the epigastrium which radiated over the chest and down both arms. He had vomited frequently and had had great difficulty in getting his breath. The pain had persisted and was still present when he was admitted to the hospital but had gradually become less severe.

The patient was very ill, prostrated, drowsy, and sweating profusely. He was propped up in bed, and there was urgent dyspnea. The breathing was Cheyne-Stokes in character. The pupils were unequal and failed to react to light. The heart was very greatly enlarged, the rate rapid, the regular rhythm disturbed by the occurrence of occasional extrasystoles. The heart sounds were distant; a systolic murmur was heard at the apex; there was proto-diastolic gallop rhythm. The peripheral vessels were not much thickened; the blood pressure was low, systolic 102, diastolic 88, at admission. There were râles in the lower lobes of the lungs; the liver was moderately enlarged and tender.

The symptoms grew progressively worse. He had paroxysms of coughing with extreme dyspnea. He became mentally confused. There was mounting fever varying between 100° and 104° F. The leucocyte count was 10,000 on admission; it rose later to 32,000. On the fifth day after admission he complained of severe pain over the lower side of the chest and in the upper part of the abdomen on the right side. A friction rub and numerous coarse râles were heard in the lower axillary area, later also at the right base. Steadily he became more and more deeply prostrated, and died seven days after entering the hospital, nine days after the onset of severe pain.

The Wassermann reaction on the blood serum was negative. The electrocardiogram showed: first degree heart block; a marked levogram; T<sub>1</sub> inverted, T<sub>2</sub> iso-



electric, T<sub>2</sub> upright, inverted T of low amplitude in chest lead; S-T<sub>2</sub> and <sub>3</sub> slightly elevated; slurring and notching of QRS complexes; P waves abnormally large in Leads II, III, and V.

From these clinical data it was confidently assumed that the terminal symptoms were due to coronary occlusion and myocardial infarction. However there was much discussion about the nature of the preceding heart disease. Since the patient did finally develop coronary occlusion most observers favored the diagnosis of arteriosclerotic heart disease. Nevertheless, some pointed out the resemblance of the symptoms to those of syphilitic myocarditis, and the possibility of syphilitic myocarditis and of myocarditis of unknown etiology was seriously considered.

At the autopsy the heart was found to be enlarged, especially the left ventricle. The apex of the heart, including the left and the right ventricles, and the lower portion of the interventricular septum were infarcted. There were mural thrombi in both ventricles. In the anterior descending branch of the left coronary artery there was a thrombus occluding the lumen. Since there was very little sclerosis of the coronary arteries and none at the point where the thrombus was located, it was concluded that the thrombus had formed about an embolus coming from the mural thrombus in the left ventricle. Moreover, microscopic examination revealed that the thrombus was not attached to the wall of the artery. Scattered through the myocardium were interlacing scars and areas of cellular infiltration similar to those seen in syphilitic myocarditis. There was very little sclerotic change in the aorta and no evidence of syphilitic aortitis. Infarcts were present in the lungs and in the left kidney. The right renal artery was occluded by an embolus.

From the clinical and pathologic records of this patient we are justified in concluding that he had had some form of myocarditis, possibly syphilitic, and that a mural thrombus had formed within the left ventricle as often happens in this condition. A fragment from this thrombus had been swept into the left coronary artery, occluding the anterior descending branch and producing an infarct in the area of heart muscle supplied by the vessel. The following case is somewhat similar.

A negro woman, 39 years of age, entered the Johns Hopkins Hospital (History No. 144964) shortly after the onset of an attack of unconsciousness with convulsions. About an hour and a half before admission, while sitting quietly at her home, she suddenly began to shake all over and cried out that she could not walk. A few minutes later she lost the power of speech and a little later still became unconscious.

According to the history of her illness she had always been well until a year before admission to the hospital, when suddenly, while at work, a queer sensation had come on above the left ear. This was followed by vomiting which recurred during the next thirty-six hours. Shortly after the vomiting had begun, the right arm and leg had become paralyzed. Function soon returned in the leg, but the arm had remained weak for months. Five months before admission she had had an attack of transient loss of speech. From then on she had been weak; she had gradually lost thirty pounds in weight, and had complained frequently of headache.

Four months before admission to the hospital she had been examined in the outpatient department. She was described as a well-developed, well-nourished woman. The pupils were regular, equal, and reacted actively to light and on accommodation. The fundi were normal except for definite sclerotic changes in the retinal arteries. The heart was a little enlarged to the left; the sounds were clear; the second aortic sound was accentuated; there was gallop rhythm. The pulse was regular, the peripheral vessels moderately thickened, the blood pressure elevated, namely, systolic

207, diastolic 130. There was a mass in the lower abdomen arising from the pelvis, evidently a myomatous uterus. The neurologic examination was negative except that the knee jerks could not be obtained.

The blood count revealed a moderate degree of anemia. The Wassermann reaction was strongly positive. The urine contained a moderate amount of albumin. The electrocardiogram had the character of a levogram; there was normal sinus rhythm.  $T_1$  was biphasic.

Upon admission to the hospital the patient was described as an obese woman in deep coma with noisy stertorous breathing. The pupils were dilated and fixed; there was external strabismus. The extremities were flaccid, the deep reflexes absent in the legs, sluggish in the arms; the Babinski test was positive on both sides. The lungs and heart could not be examined satisfactorily on account of the noisy breathing. The blood pressure was, systolic 220, diastolic 120. The spinal fluid was grossly bloody; the cell count gave 100,000 red corpuscles and 320 leucocytes, of which 68 per cent were polymorphonuclears.

After admission to the hospital the temperature rapidly rose and finally reached 109° F. The coma deepened, and the patient died ten hours after entry.

At autopsy the heart was found to be enlarged. Mural thrombi were present in both ventricles and in the right auricular appendage, and emboli were discovered in the basilar artery, the meningeal arteries, the left anterior cerebral artery, the splenic artery, and the coronary arteries. The coronary arteries showed small plaques of sclerosis here and there, but the degree of sclerosis was slight. Thrombi were found in the right coronary artery, and in the anterior descending branch of the left coronary artery, with infarctions at the apex of the heart and in the posterior portion of the ventricle behind the mitral valve. There was chronic passive congestion of the liver and conspicuous sclerosis of the arterioles in the kidneys, pancreas, and elsewhere.

In this patient no doubt enlargement of the heart had followed upon hypertension; as often happens, mural thrombi formed in the enlarged heart; from these thrombi had come the emboli which had lodged in the arteries of the brain, in the splenic artery, and in the coronary arteries.

##### *5. Coronary emboli coming from thrombi in the pulmonary veins*

When we consider the great frequency of pulmonary infection we might anticipate that thrombosis of the pulmonary veins would occur commonly and that particles of clot dislodged from these thrombi would be a fertile source of embolic phenomena in the systemic circulation. However, experience teaches us that this is not the case. Embolism in pneumonia is very rare. The reason for this unexpected failure to observe the symptoms of embolism in pneumonia is the fact, well known to pathologists, that thrombosis of the pulmonary veins does not take place. Only when there is suppuration or invasion of the veins by tumor does thrombosis of the veins occur. In association with suppurative disease and carcinoma of the lung embolism is not uncommon; brain abscess in the one case and cerebral metastases in the other are frequent complications. Although venous thrombosis does not occur in uncomplicated pneumonia, nevertheless areas of suppuration frequently accompany and follow pneumonic inflammation, and it must be that often these areas are too small to be detected clinically and heal without the appear-

ance of betraying symptoms. Therefore I remain surprised at the infrequency of embolic manifestations in the course of pneumonia. I know of only two instances in which an embolus plugging a branch of a coronary artery has been demonstrated to have come from the pulmonary veins.

Medlar reports the post-mortem studies on a man, 40 years of age, who had been ill with pulmonary tuberculosis for six months, yet not ill enough to have been confined to bed. On the day of death he was up and about as usual. While walking he collapsed and died immediately. The autopsy revealed bilateral pulmonary tuberculosis and a small cavity in the right upper lobe. There was recent infarction of the lateral and upper portion of the left ventricle, the infarct measuring 3 cm. in length and 1.5 cm. in width. The valves of the heart and the endocardium were normal. The coronary arteries were healthy. No thrombus was discovered on gross inspection. Microscopic examination of sections disclosed in the neighborhood of the infarcted area a branch of the coronary artery plugged by a mass of caseous material containing numerous tubercle bacilli. There was no evidence of tuberculosis in the tissues about the artery, and tubercle bacilli could not be found in these tissues.

The case observed at the Johns Hopkins Hospital is unusually interesting and apparently unique; therefore I report the records in greater detail.

A white man, an engine stoker, 57 years of age, entered the Johns Hopkins Hospital Oct. 18, 1932 (History No. 45924), complaining of weakness and stomach trouble. Until three years before, when his illness had begun, he always had been a strong, healthy man, boasting that he had never been sick a day in his life. The illness had come on suddenly. One afternoon, probably an hour after his midday meal, suddenly he was seized with excruciating pain in the abdomen just below the xiphoid cartilage. He sweated so profusely that his clothes were soaking wet. The pain continued the whole afternoon and was so severe that he was like a "crazy man" as he expressed it. At 9 o'clock that evening a physician arrived who gave him two hypodermies, but with relatively little benefit. The pain continued during the night until the following morning at four o'clock, when he vomited profusely, and after this he felt immediate relief. Preceding the vomiting the abdomen had been blown up with gas. Following this event he had some fever and was very much prostrated. He was obliged to remain in bed for four weeks. When he got up he went about quietly for another week and then returned to work. His work was heavy, and he had great difficulty in carrying it on because he felt very weak, and also now for the first time he began to notice marked shortness of breath on effort. After a few weeks he was obliged to give up. He tried again and again to work but on each occasion he could keep at it for only a week or two, and then he had to stop on account of weakness and shortness of breath. A few months before coming to the hospital he had caught a cold. This brought on cough with dark sputum which often was streaked with blood. The cough continued, his shortness of breath grew worse, and he had been obliged to spend most of his time in bed.

*Examination.*—His temperature was 100.4° F., pulse, 76, respiration 22, blood pressure, 126/100. The patient was a fairly well-nourished man who evidently had lost much weight. He was propped up in bed with moderate dyspnea. He had frequent attacks of coughing but raised very little expectoration. The skin and mucous membranes were rather pale. The eyes were normally prominent. The extraocular movements were normal. Pupils were equal, regular, reacted actively to light and on accommodation. The fundi showed practically normal conditions,

only a slight degree of sclerotic change in the arteries. The teeth were worn and many were carious; there were a number of old stumps. The gums were in fairly good condition. The throat showed nothing remarkable. A number of the cervical and axillary lymph nodes were palpable, but there was no marked lymph node enlargement. The thyroid was of average size and normal consistency. The chest was long and narrow with diminished expansion on the right side. On the right there was flatness below the level of the fourth rib in front and below the angle of the scapula in back. Over this area the breath sounds were greatly diminished in intensity, and there was typical egophony. At the upper border of dullness the breath sounds were tubular in quality, and many moist râles were heard. The apex beat of the heart was in the fifth intercostal space, 11 cm. from the midline. Cardiac dullness to the right could not be ascertained on account of the pulmonary dullness. It extended 13 cm. to the left. The heart sounds were clear; the second aortic was louder than the second pulmonic. The pulse was equal at the two wrists. The vessel walls were moderately thickened. The blood pressure varied a little in the two arms—right 112/84; left 126/100. The abdomen was distended. It moved freely with respiration. A mass was felt in the right upper quadrant extending 6 cm. below the costal margin. This seemed certainly to be the liver although a lower border could not be felt on account of the tenseness of the abdominal wall. There was edema of the ankles and over the tibiae up to the knees. There was a little edema over the sacrum. Genitalia showed no abnormality except slight edema of the scrotum and prepuce. Rectal examination showed an enlarged, hard prostate but otherwise was negative. Neurologic examination revealed no abnormality.

*Course in the Hospital.*—The right pleural cavity was tapped on the day of admission, and 1300 c.c. of cloudy fluid were withdrawn. Following this the patient was more comfortable. The physical signs over the right lower lobe now suggested that there was consolidation of the lung as well as pleural effusion, and a roentgenogram taken two days later confirmed this impression. The fluid recurred promptly and the pleural cavity frequently was tapped. All of those who examined the patient thought there was evidence of pulmonary infiltration as well as of fluid at the right base. This pulmonary infiltration was thought to be either carcinoma or pulmonary infarction. The roentgenogram at first favored the diagnosis of carcinoma but the shadow gradually decreased in size and finally almost completely disappeared. The physical signs over the chest also changed; at the beginning of December there were only dullness and diminution in the intensity of the breath sounds over the right lower lobe. With this improvement in the pulmonary condition there was simultaneous improvement in his general condition. He gradually lost his dyspnea and by the beginning of December he felt so well that he was eager to be out of bed. The wide area of cardiac dullness to the left, present when the patient entered the hospital, was due apparently to dislocation of the heart to the left by the pleural effusion. After the effusion disappeared the heart returned to its normal position but was still definitely enlarged. From time to time the heart's action was irregular due to the occurrence of numerous extrasystoles. During the first month that the patient was in the hospital he had a good deal of cough and raised small amounts of mucoid sputum which frequently was streaked with blood. On Dec. 16, 1932, the note was made "the patient is much improved and is getting up as desired." He still had some cough but very little sputum. There were still dullness and diminution in intensity of the breath sounds over the right lower lobe. A little swelling of the ankles persisted.

On the morning of Dec. 20, the patient awoke with rather severe pain over the heart and shortness of breath. The symptoms of myocardial insufficiency recurred and grew gradually more and more severe during the day. A proto-diastolic gallop was heard at the apex; the heart sounds were distant and feeble; the pulse was thready and the blood pressure fell to systolic 90, diastolic 60. A definite pleural friction was heard over the front of the left chest. During the next night he be-

came progressively worse. His pulse became weaker, his respirations very irregular and gasping. There was extreme cyanosis; his face looked drawn and had an ashen hue. He sweated profusely. On the morning of Dec. 21, he was pulseless and comatose. The friction rub over the left lower chest became more pronounced and breath sounds in that area were suppressed. His condition grew steadily worse; the pulse disappeared at the wrist and the blood pressure was so low it could not be estimated. A little after midnight on Dec. 22 he died quietly.

The blood counts were normal. The Wassermann reaction was negative. The urine on admission had a normal range of specific gravity; it contained a large amount of albumin and many casts. Later albumin disappeared and only an occasional cast was found. The electrocardiograms showed sinus rhythm, usually regular, at times disturbed by ventricular extrasystoles; delayed auriculoventricular and intraventricular conduction, left bundle branch block. The measurements of the teleroentgenogram were: M. R. 9; M. L. 9.3; A. 9.2; T. 28.7.

From the autopsy record the following excerpts are made:

*Anatomic Diagnosis.*—Thrombosis of anterior descending branch of left coronary artery. Scarring of myocardium. Scarred sacculated infarct of left ventricle covered by large thrombus somewhat organized. Thrombus at tip of right ventricle. Cardiac hypertrophy and dilatation. Pericardial adhesions at apex. Thrombi in branches of pulmonary artery, right and left lower lobes. Infarcts in lungs. Hydrothorax left, 400 c.c. Chronic passive congestion of lungs, liver, and spleen. Lobular pneumonia. Empyema at the base. Arteriosclerosis of aorta. Atrophy and scarring of pancreas. Slight scarring of kidneys. Enlargement of thyroid with colloid adenomata. Benign prostatic hypertrophy, slight. Caseous lymph nodes at hilum of right lung. Pleural adhesions, right. Hemorrhoids, internal.

The heart is enlarged, the enlargement due chiefly to dilatation of left ventricle. Weight was 600 grams. Epicardium is smooth and glistening except over the apex where there are dense adhesions between the layers of the pericardium over an area about 3 by 4 cm. on the anterior surface of the left ventricle. Almost the entire wall of the left ventricle anteriorly is covered by a large thrombus which at the apex measures 3 cm. in thickness. This appears to be relatively old and undergoing organization. At the tip of the right ventricle a fresher thrombus is adherent to the endocardium, measuring 1.5 by 1 cm. The valves are all delicate and competent. The myocardium contains a few small scars near the base. At the apex of the left ventricle the wall is distinctly thinned and the myocardium appears to be replaced by dense fibrotic tissue. This covers practically all of the apex and extends upward about halfway to the base of the heart. The right ventricle appears to be normal except for a small area at its tip which is covered by the small thrombus mentioned above. The mouths of the coronary arteries are not obstructed. About 2 cm. from the origin of the anterior descending branch of the left coronary there is an old thrombus apparently undergoing organization. It practically occludes the lumen of the artery. No sclerosis of the coronary arteries is anywhere visible, and the arteries are delicate and straight.

The left lung weighs 750 grams. Its external surface is smooth and normal in appearance. At the tip of the lower lobe, anteriorly, there is a thrombus in the small branch of the pulmonary artery leading to a fresh infarct; elsewhere the lung is air-containing and normal in appearance. The right lung is removed with difficulty because of firm adhesions to the diaphragm and costal pleura, and the posterior portion of the lower lobe is torn away and left firmly attached to its overlying pleura. The pleura in this area is greatly thickened and between its layers is a collection of about

25 c.c. of pus. The upper and middle lobes show nothing abnormal on section. The posterior portion of the lower lobe does not contain air. It is black in color and rubbery in consistency. A large branch of the pulmonary artery leading to it is found to contain a rather old thrombus, organizing and extending 3 or 4 cm. along its course. About the bronchi there is a collection of moderately enlarged lymph nodes which show patches of calcification on section.

*Microscopic notes.*—Section through the coronary artery shows a perfectly normal delicate structure without arteriosclerosis. A section taken a little further down shows a partly organized thrombus which nearly occludes the lumen of the artery.

A section taken through the wall of the left ventricle shows marked scarring of the myocardium with gradual dwindling of the muscle fibers as the thrombosed area is approached, where the scarring becomes more pronounced. Finally the muscle fibers are replaced by a firm dense scar over which lies the old thrombus now become fairly well organized and laminated and covered with a fresher thrombus. Section taken through the mitral valve shows some hypertrophy of muscle fibers and some slight scarring of the myocardium. The valve, the epicardium, and endocardium are normal.

One section of the lung shows an organized thrombus in the branch of the pulmonary artery; another section shows a hemorrhagic infarct. In other places there are areas of lobular pneumonia which contain Gram-positive diplococci. There is marked chronic passive congestion of the lung and many alveoli are filled with mononuclear cells containing blood pigment. Another section shows an old abscess, very well encapsulated between the two layers of the pleura. There is some organization.

In this instance the evidence that the coronary occlusion was due to an embolus and not to arteriosclerosis seems to me to be incontrovertible. No origin for the embolus was found other than the pulmonary abscess, and since the existence of a relation between the two is an altogether reasonable supposition, we are warranted in assuming that the embolus came from that source.

#### 6. *Coronary emboli coming from thrombi in the systemic veins*

Paradoxical embolism does not occur frequently; therefore, I was surprised to find it reported four times among the thirty-eight collected cases of coronary embolism, an incidence of over 10 per cent. It is unbelievable that this high incidence represents a true proportion, and no doubt it is explained by the fact that, since paradoxical embolism is rare, most instances that are observed are reported, whereas commoner forms of coronary embolism are not deemed worthy of such particular notice.

Wolff and White mention the case of a woman, 43 years of age, with carcinoma of the ovaries. Suddenly she fainted and shortly after died. Autopsy revealed thrombosis of the pelvic veins, embolism of a patent foramen ovale, and embolism of the descending branch of the left coronary artery.

Thompson and Evans report about a young man, 25 years of age. Five days before entering the hospital, while at work, suddenly he had fallen unconscious and thereafter had never properly rallied. He died about half an hour after admission to the hospital. The hasty examination disclosed coma, stertorous breathing, left hemiplegia. At the post mortem there were a malignant teratoma involving both testes; a mass of growth projecting through the patent foramen ovale; a large

polypoid mass of growth projecting from the wall of the left ventricle and a similar mass free in the left ventricular cavity; growth emboli in both coronary arteries and in the right middle cerebral artery.

Saphir reports the case of a man, 35 years of age, admitted to the hospital with bronchopneumonia. The pneumonia spread and auricular fibrillation came on. A few days later the right femoral artery became occluded followed by gangrene of the foot. At the end of three weeks the leg was amputated between the middle and lower third of the femur. The patient recovered from the operation and convalescence was proceeding uneventfully when on the seventeenth postoperative day he died suddenly.

At the autopsy was found diffuse sclerosis of the aorta. At the bifurcation there was an atheromatous ulcer covered by a thrombus. An embolus completely occluded the right femoral artery. The right femoral vein was filled with thrombus which extended into the iliac vein. The heart was enlarged. The right auricle contained an embolus which extended into the right ventricular cavity. The foramen ovale was patent. An embolus occluded the descending branch of the left coronary artery. The intima of the coronary arteries was smooth, without evidence of sclerosis. In the lungs there was organizing bronchopneumonia. Many of the smaller branches of the pulmonary artery in both lungs were plugged by emboli.

The patient reported upon by Mendel, Kenler and Silverman was a woman, 47 years of age. Six days before admission to the hospital she had been taken ill with vague pains and aches diagnosed as grip. A few days later she developed vomiting, diarrhea, and abdominal cramps. She was a well-developed, well-nourished woman. The physical examination revealed no noteworthy abnormality. There were no cardiovascular symptoms and the heart was quite normal. On the sixth day in hospital she was seized suddenly with sharp, agonizing pain under the sternum and fifteen minutes later was dead.

At the post-mortem examination the heart appeared to be normal except that the foramen ovale was patent, the opening measuring 0.5 cm. in diameter. The valves were unaffected, and there were no thrombi in auricles or ventricles. The anterior descending branch of the left coronary artery was occluded by a soft lamellated gray-red thrombus, 1 cm. in length and 0.3 cm. in diameter. The thrombus was easily removed, disclosing the underlying intima which was smooth, glistening, and utterly devoid of atheromatous change. The coronary arteries throughout the heart were equally normal in appearance. In the aorta there were a few small yellowish patches of atheroma, but the intima over these, as elsewhere, was smooth and glistening. There was no slightest evidence of syphilis. The left femoral vein was plugged by a firm brownish clot which at its proximal end, near the entrance to the iliac vein, was continued as a grayish-red softer thrombus, similar in appearance to the one found in the coronary artery. There was slight pitting edema over the whole left leg and the sacrum, a fact which had been overlooked clinically.

### *The Clinical Features of Coronary Occlusion Produced by Large Coronary Emboli*

From this brief review of observed cases of coronary embolism it is apparent that the symptoms of this condition are characteristic of those of coronary occlusion from whatever cause. It would be impossible even to venture the diagnosis from any particular differences in the symptoms. There is only one special feature that has been commented upon, namely, that in most cases death is very sudden, indeed instantaneous. This is explained by the fact that coronary embolism has no rela-

tion to disease of the coronary arteries and therefore will occur often when the coronary arteries are healthy and the heart unprepared, by the gradual development of an efficient collateral circulation, to withstand the effects of occlusion of a large branch. Nevertheless this feature is not sufficiently distinctive to be helpful in diagnosis. For purposes of diagnosis we must depend upon suggestions that may come from the whole clinical setting in which the accident occurs.

One of the important elements of this setting is the age of the patient. Coronary thrombosis secondary to atherosclerosis occurs seldom before forty years of age. I am well aware of the fact that a large number of cases are now on record which have come on in the thirties and many even in the twenties. However, cases occurring at an early age attract comment and are often reported. In the hope that I might find evidence to justify the suspicion that some of the cases of coronary occlusion affecting young persons may have been due to embolism and not to arteriosclerosis, I reviewed the details of many records in the literature. I was unable to find the evidence I sought. Many of the patients recovered and although the clinical records left no reasonable doubt about the accuracy of the diagnosis of coronary occlusion, still, in the absence of anatomic study, the nature of the mechanism of occlusion could only be surmised. In another large group of cases, the post-mortem findings are only briefly and incompletely reported so that the cause of the occlusion is not clearly demonstrated. In the remaining cases the results of the autopsy are given in sufficient detail to establish with reasonable security that the cause of the occlusion was coronary arteriosclerosis. Nevertheless it must be admitted that even anatomically the diagnosis of coronary embolism is difficult and that only rarely will it be made unless the evidence supporting that diagnosis is carefully searched for. The experience at the Johns Hopkins Hospital recurs to me again. Judging from the records of the Pathologic Department the diagnosis was not recorded during a period of over fifty years, but once having been made it was repeated ten times during the following nine years. Therefore it is reasonable to anticipate that when pathologists examine cases of coronary occlusion with the possibility of embolism prominently in mind, more and more instances of this condition will be recognized.

The occurrence of coronary embolism when the embolus is a thrombus or atheromatous material from the coronary artery itself has no clinical interest. Coronary occlusion due to emboli coming from thrombi covering plaques of sclerosis in the wall of the aorta presents an almost impossible problem in diagnosis. Five of the six patients reported were from 24 to 35 years of age, averaging 30 years. Sudden death occurring in a young person who had previously been healthy might awaken a suspicion of coronary embolism from that source but the diagnosis could not be differentiated from coronary thrombosis due to coronary sclerosis. Coronary embolism would be suggested immediately were a patient with bacterial endocarditis to die suddenly. Sudden death in bacterial endo-



carditis is usually due to coronary embolism or the rupture of a mycotic aneurysm into the pericardial cavity but sometimes even at autopsy no gross cause for the sudden death is discovered. Cerebral embolism or the rupture of a mycotic aneurysm elsewhere than into the pericardial cavity is seldom instantaneously fatal. If from the clinical manifestations we are able to conclude that a patient with heart disease has a mural thrombus within the left auricle or ventricle we would suspect that coronary embolism had occurred were he to die suddenly. I have already expressed surprise that coronary emboli coming from thrombi in the pulmonary veins have been observed so very seldom. On a number of occasions I have examined patients in the thirties or early forties who have had coronary occlusion followed by perfect and long continued recovery and have suspected that the occlusion may have been due to an embolus coming from this source. However, no confirmation of the supposition could be obtained. Perhaps more cases will be found when they are carefully looked for. Coronary embolism might be predicted in a patient having thrombophlebitis and dying with the characteristic symptoms of coronary occlusion. However, a confident distinction from pulmonary embolism would be difficult.

Although to diagnose coronary embolism correctly might confer academic satisfaction and distinction, it is pertinent to ask what consequences of benefit to the patient could possibly follow from the diagnosis. As far as I can see there is only one. I have already commented upon the fact that when an embolus occludes a large branch of a coronary artery, death is usually instantaneous because the coronary arteries are healthy; for the same reason if a patient recovers from the effects of coronary embolism the chances are good that recovery will be complete and permanent, for there is no reason to fear a repetition of the accident, and the remaining heart muscle is healthy and abundantly nourished. In a word, whereas the immediate prognosis is bad, if the patient lives the ultimate prognosis is good. This being the case, were we able to say with assurance that coronary occlusion had been due to embolism we could look to the future with encouraging confidence, and restrictions upon activity need be less severe.

At the present time the diagnosis of coronary embolism is extraordinarily difficult and I doubt that it can be made definitely except under unusual circumstances. Nevertheless if in differential diagnosis we bear it in mind we shall see many cases in which this possibility must be carefully considered and perhaps in time we may learn to recognize distinguishing features. To make my meaning clear I shall cite an illustrative case.\*

In November, 1938, I saw upon the wards of the Cincinnati General Hospital, with Dr. Marion A. Blankenhorn and Dr. Johnson McGuire, a young woman, 34 years of age, who was in the fifth month of pregnancy. She was an overnourished

\*I am indebted to Dr. Blankenhorn for permission to report this case and to Dr. W. B. Bean for a summary of the hospital records.

woman having the appearance of robust, vigorous health. She felt well and the physical examination revealed no abnormality. The heart was not enlarged; the sounds were clear and of normal quality except for the presence of a soft systolic murmur. The pulse was slow and regular, the peripheral vessels soft, the blood pressure, systolic 132, diastolic 60. The electrocardiogram was essentially normal. The patient had been admitted to the hospital for a decision upon the advisability of interrupting pregnancy. In order to appreciate the pertinency of this question it is necessary briefly to review the records of previous admissions to the hospital.

March 30, 1927, admitted to the obstetrical service and the following day was delivered spontaneously of a healthy child.

Aug. 10, 1928, again admitted to the obstetrical service and the same day gave birth spontaneously to a healthy child. During the latter months of pregnancy had had a little edema of the ankles and a little shortness of breath.

On Dec. 25, 1930, was admitted to the surgical service. A diagnosis of gall stones and cholecystitis was made. On this occasion as well as on the two previous admissions no evidence was found of the slightest abnormality in the heart. Patient left the hospital but a little later cholecystectomy was performed at another hospital.

April 8, 1937, she entered the hospital on the medical service complaining of shortness of breath, cough, and swelling of the ankles. She had been well until eleven days before admission when she began to have pain in the right upper quadrant of the abdomen. She felt chilly and later feverish. The following day the pain spread over the front of the chest on both sides and cough and expectoration developed. On the fifth day after the onset of the illness, at a time when she was still in bed, though feeling much better, she was suddenly taken with severe shortness of breath and palpitation. The dyspnea steadily increased; she had paroxysms of coughing and raised frothy expectoration; later edema appeared about the ankles and gradually spread to the legs.

On admission the temperature was 99.6° F., the pulse 106, the respirations 30, the blood pressure 158/124. She was a well-developed and well-nourished woman propped up in bed, with great shortness of breath. The apex beat of the heart was in the sixth intercostal space 10 cm. to the left of the midline. The area of cardiac dullness measured 3.5 cm. to the right and 10.5 cm. to the left. The heart sounds were described as being of poor quality and some observers heard a soft systolic murmur. There was decided proto-diastolic gallop rhythm. The pulse was regular, the peripheral vessels soft, only slight arterial changes in the ocular fundi. The peripheral veins were distended, and there was slight cyanosis. The legs were swollen with edema. Numerous moist râles were present over the lower lobes of the lungs and at the right base there were signs of consolidation. The liver was a little swollen and tender.

Under treatment with digitalis the edema and shortness of breath soon disappeared, the slightly elevated temperature fell to normal, and the signs of consolidation at the right base cleared. Successive electrocardiograms revealed changes characteristic of an anterior infarction.

The patient left the hospital without symptoms and in good condition.

For a year after discharge from the hospital she continued to take digitalis and during this period led an active life and was well. At the end of the year there seemed to her to be no reason for continuing digitalis, and therefore she stopped taking it. Late in June or early in July, 1938, she became pregnant and when she appeared at the prenatal clinic in October, her previous records were reviewed, and on account of the symptoms of heart failure that had been observed and diagnosed as coronary occlusion during her stay in the hospital a year and a half before, she was again admitted for consideration of the advisability of interrupting the pregnancy.

With these records and observations before us the diagnostic problem was an interesting one. A healthy young woman, 33 years of age, during the course of a respiratory infection is taken suddenly with severe shortness of breath and palpitation followed by the typical symptoms of congestive failure. These symptoms soon subside and recovery is seemingly complete since the patient was able to lead a very active life without the least discomfort. A number of examinations made before the attack of heart failure had occurred, and a very thorough investigation made a year and a half after the attack, had failed to show the slightest evidence of disease of the heart. This brief period of heart failure in a healthy young woman, coming on abruptly and leaving after it no sign of permanent damage to the heart, can best be explained as evidence of coronary occlusion. The electrocardiographic changes support this conclusion. Therefore assuming that the patient had had coronary occlusion we stopped to consider the cause of the occlusion. There was no direct evidence to justify a diagnosis of coronary arteriosclerosis, and yet it is well known that even advanced coronary arteriosclerosis may exist in the absence of any signs that might betray its presence. Moreover coronary sclerosis need not be advanced to cause occlusion of an arterial branch; thrombosis may follow the rupture of an isolated atheromatous ulcer and the rest of the coronary arteries show only insignificant change. Nevertheless under the circumstances it was not unreasonable seriously to consider the possibility that the occlusion might have been caused by an embolus. The fact that the cardiac symptoms had come on suddenly as an acute respiratory infection was subsiding suggested that the embolus, if it was an embolus, had come from a thrombus in the pulmonary veins. Could one be sure that the occlusion had been caused by an embolus there would be no threat of further damage to the heart and with this assurance there could be no hesitation in deciding to allow the pregnancy to proceed. I do not mean to imply that considering all of the circumstances the decision necessarily would have been in favor of terminating the pregnancy had it been possible to establish the diagnosis of coronary thrombosis on the basis of arteriosclerosis, but merely that the possibility of coronary embolism was a factor in arriving at the conservative decision.

The pregnancy proceeded uneventfully, and on March 31, 1939, the patient was delivered of a healthy, full-term child. Since leaving the hospital she has been observed regularly in the cardiac clinic. She has remained well, and no slightest abnormality has been detected in the circulatory system.

I wish to emphasize that I report this case not as an instance of coronary embolism but merely as an illustration of the sort of circumstances under which the possibility of coronary embolism should seriously be considered.

## II. CORONARY EMBOLI OCCLUDING SMALL BRANCHES OF THE CORONARY ARTERIES

The occlusion of small branches of the coronary arteries produces scarring of the heart, and if many small branches are occluded, the scarring may become widespread and seriously impair cardiac efficiency. In contrast to the dramatic symptoms which usually follow occlusion of large coronary branches, the obstruction of small branches proceeds unnoticed. Only after large portions of the heart muscle have been destroyed, do symptoms appear, and these symptoms are the usual ones of heart failure which are in no way distinctive of coronary disease. The diagnosis of myocardial scarring due to coronary disease is reached by a circuitous path of reasoning and inference. In the presence of heart failure, to begin with, we must eliminate valvular defects, hypertension in the general circulation and in the pulmonary circulation, pericardial adhesions or effusion, and congenital anomalies as the cause of the failure. If by this process of elimination we arrive at the conclusion that disease of the heart muscle is the essential cause we must then proceed by a careful consideration of all the evidence at hand to decide upon the nature of the underlying myocardial disease. In the absence of heart failure certain disturbances of rhythm, for instance heart block, and abnormalities in the electrocardiogram furnish important evidence of damage to the heart muscle. After we are reasonably sure that the heart muscle is seriously injured and that the cause of the injury is impairment of the coronary circulation, we may then attempt to decide whether the impairment is due to diffuse coronary arteriosclerosis or to the obliteration of many small coronary branches by emboli. In reaching this final decision we are guided not only by an examination of the circulatory system but also by a careful consideration of all the associated manifestations of the illness. The two conditions with which we observe multiple coronary emboli are bacterial endocarditis and intracardiac thrombi.

I have pointed out that bacterial endocarditis is the usual source of emboli which plug large branches of the coronary arteries. However, such large emboli lodge in the coronary arteries in only a relatively small number of the cases. In contrast to this, numerous small emboli enter the coronary circulation almost invariably. Evidence of their presence is seldom missed when sections of the heart muscle are examined under the microscope. Recently de Navasques very thoroughly studied the hearts from twenty cases of *Streptococcus viridans* endocarditis. In all but one he found evidence of coronary embolism. Saphir reports finding small organizing infarcts in twenty-eight of thirty-five unselected cases.

These small coronary emboli produce no symptoms by which their presence may be recognized. Apparently they bear no definite relation to the degree of myocardial insufficiency. Patients with bacterial endocarditis usually die of the infection or complications, seldom of myo-

cardial insufficiency. In the rare cases in which death is caused by heart failure it would be interesting to examine carefully the heart muscle to determine to what extent myocardial damage, due to coronary emboli, had contributed to the failure.

I have already cited the figures of Garvin indicating that at autopsy mural thrombi are found in the left side of the heart in 25 per cent of all cases in which death is caused by heart failure. Clinicians are thoroughly familiar with the embolic manifestations that come from these thrombi and guided by these symptoms are able to predict their presence. As I have pointed out, large emboli occasionally lodge in the coronary arteries, producing the characteristic symptoms of coronary occlusion. In a large number of the cases small emboli reach the coronary circulation and sometimes in such profusion as seriously to damage the myocardium and in this way precipitate heart failure. It is true that there must be some antecedent disease of the heart for mural thrombi to form, but often this disease is of a nature not seriously to impair its function. The symptoms of heart disease and the final failure may all be due to the emboli discharged from the mural thrombus. Clinicians seem not fully to have realized the importance of numerous small coronary emboli as a cause of heart failure. At the Johns Hopkins Hospital the matter has been called to our attention again and again by Dr. Rich at clinical-pathologic conferences, and during the past few years on a number of occasions we have correctly predicted that the autopsy would reveal the presence of these lesions.

In describing large coronary emboli coming from mural thrombi I cited a case of multiple infarcts of the heart. In concluding I will report briefly another instance in which numerous small emboli led to extensive myocardial fibrosis.

A Polish steel worker, 45 years of age, entered the Johns Hopkins Hospital Jan. 27, 1939 (History No. 162602), complaining of pain in the abdomen and over the heart. Three years before over a period of a month he had complained constantly of pain about the heart. There had been no other symptoms. His physician had told him his heart was enlarged. In other respects he had always been well. The illness that brought him to the hospital had begun three months before, when he had been taken suddenly with severe pain in the right lower quadrant of the abdomen. He had entered the Church Home and Infirmary where his appendix had been removed. He made an uneventful recovery and returned to his work. Two weeks before admission he began to have pain in the upper part of the abdomen and also over the heart. The pain had continued intermittently. With the onset of pain there had been shortness of breath, and this gradually had become more and more severe. The important points in the physical examination were these: Well-developed man of healthy appearance, moderately dyspneic. Only a little cyanosis. The heart was considerably enlarged, particularly to the left. The heart sounds were distant and faint but no murmurs were heard. There was definite gallop rhythm. Pulse was regular, rapid, of small size. No evidence of sclerosis of the peripheral or retinal arteries. Rales of edema over the lower lobes of the lungs, an enlarged tender liver, and a little subcutaneous edema at the ankles and over the sacrum.

The patient spent four months in the hospital. He improved very slowly. On March 24, he had an attack of weakness and dizziness followed by a period of mental confusion. On discharge from the hospital on May 28, 1939, he was somewhat better but it was clear that he had little cardiac reserve. The blood pressure was systolic 115 to 154, diastolic 95 to 124. The pulse pressure was always low. The electrocardiogram on admission showed a levogram with tendency towards low voltage.  $T_1$  and  $_2$  were inverted. There was slurring of QRS<sub>1</sub> and  $_2$ .

Patient entered the hospital again Dec. 12, 1939. During the seven months intervening between his previous discharge and this admission the patient had got on reasonably well but was always short of breath and complained often of pain about the heart. Early in November distressing attacks of nocturnal dyspnea had begun to occur. From then on there was increasing shortness of breath and later swelling of the ankles. The examination on this occasion showed decided dyspnea and cyanosis was pronounced. The veins in the neck were engorged. The heart was more enlarged than on the previous admission, the heart sounds were faint; no murmurs were heard; the second pulmonary sound was accentuated. Pulse was regular and rapid; there was no unusual sclerosis of the peripheral or retinal vessels. Râles of edema were heard over the lower lobes of the lung, and in the right pleural cavity there was a small effusion. There was now definite ascites. The liver was swollen.

After admission to the hospital the patient had considerable fever for which no explanation was found. He was always short of breath and complained of pain over the engorged liver. The venous pressure was 250 mm. of water, on another occasion 276. The patient was delirious and the delirium became more pronounced. On Dec. 30 it was noticed that the left leg was cold below the knee and the skin mottled. No pulsation could be felt in the arteries of the leg. From then on Cheyne-Stokes breathing became more pronounced with long periods of apnea, the lungs filled with coarse bubbling râles and the following day, Jan. 1, 1940, the patient died.

The important facts from the records of the autopsy are as follows:

*Anatomic Diagnosis.*—Moderate generalized and coronary arteriosclerosis. Diffuse myocardial scarring. Mural thrombus left ventricle. Cardiac hypertrophy and dilatation. Multiple emboli, left femoral, mesenteric, right renal, cerebral and pulmonary arteries. Old and recent infarcts of spleen. Recent infarct of right kidney. Encephalomalacia. Purulent bronchitis and lobular pneumonia, lower lobes of both lungs.

The heart is moderately enlarged, weighing 590 grams. Left side dilated and hypertrophied, right side dilated. The epicardium is smooth. Valves are all delicate and competent. In the left ventricle is a large, oval thrombus attached to the interventricular septum, extending upward from the apex for a distance of about 7 cm. The musculature of the left ventricle is firm except that in the posterior wall there are areas of contrasting softness. In the root and ascending arch of the aorta there are a few small sclerotic plaques which do not encroach upon the mouths of the coronary arteries. The large branches of the coronary arteries show a few small scattered arteriosclerotic plaques. There is no narrowing of the lumen of the arteries. The right coronary artery is somewhat longer and wider than usual and it is somewhat more sclerotic than the left.

*Microscopic Notes.*—All the sections of the heart show rather pronounced myocardial scarring. This is of two distinct types, one diffuse and consisting of strands of scar tissue between muscle fibers, the other circumscribed and consisting of large areas in which the muscle tissue has been replaced by scar tissue. Near these large scars occluded blood vessels are seen, the occlusion probably due to emboli.

Several sections of the right and left coronary arteries show a moderate degree of sclerosis with thickening of the wall but only slight narrowing of the lumen.

The heart of this patient showed diffuse interlacing scar tissue, evidently the result of a preceding myocarditis of unknown etiology. The myocarditis was the primary disease but since at autopsy only diffuse scarring remained to reveal that it had been present it evidently was not responsible for the heart failure. Once the thrombus had formed in the left ventricle it became the source of subsequent symptoms; not only of the numerous embolic manifestations that occurred, but also of the heart failure itself which undoubtedly was due, at least chiefly, to numerous small coronary emboli.

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## BLOOD VOLUME AND CARDIOVASCULAR ADJUSTMENTS

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I MUCH appreciate the honor of succeeding my two distinguished predecessors in this lectureship. Both of your previous lecturers have considered problems involving fluid balance. Today I propose to consider the blood in its relation to the circulation. Certain simple axioms may be stated—so simple that we shall all be in agreement. Certain definite clinical facts are established. Beyond these we pass into a region of conjecture and hypothesis, where our knowledge is very incomplete. In this field, clinical observation and physiologic investigation may together clarify the situation, but either of these alone has little chance of finding any real solution.

The most obvious axiom is the fact that the blood volume and the capacity of the vascular bed must always be the same. The elastic vascular bed may be distended at a greater or less pressure, but empty spaces are unthinkable. We are all familiar with the marked variations in vascular tone, of shorter or longer duration, that may develop. We are all likely to forget that any such change in the size of the vessels must be associated with a corresponding change in blood volume, unless the circulatory system is so regulated that any enlargement of one set of vessels is exactly balanced by an equal reduction in the size of other vessels. Although such a reflex control does probably play the major role in rapid adjustments, alterations in blood volume appear to be part of the normal mechanism. These alterations in blood volume are to meet the demands of an altered vascular bed.

We may also accept as axiomatic Starling's<sup>1</sup> hypothesis of fluid balance. The osmotic forces exerted by colloidal plasma proteins which attract fluid into the capillaries balance the filtrating forces created by capillary pressure. More recent investigations of this balance from very different angles include work by Landis<sup>2</sup> and Gregersen and Stewart.<sup>3</sup> In the past, tissue fluid pressure has been considered negligible; at the present time we know that this is not the case.<sup>4</sup> The differences in hydrostatic pressure between the capillaries and the tissue spaces are none the less balanced by the differences in colloidal osmotic pressure between the plasma and tissue fluid. With this slight modification, Starling's hypothesis still stands, and it seems unlikely that it will ever be seriously challenged. On Starling's hypothesis, the volume of the blood plasma is determined by the total amount of plasma proteins

<sup>1</sup>The George Brown Memorial Lecture, delivered at the sixteenth annual meeting of the American Heart Association, New York, June 8, 1940.

<sup>2</sup>From the Department of Physiology, Medical School, University of Pennsylvania.

<sup>3</sup>Received for publication June 17, 1940.



circulating in the vessels, for this quantity determines the volume of fluid that can be maintained in the system with a balance at a normal pressure level. We know full well that, after a moderately large hemorrhage, this quantity of protein is reduced and may not return to normal for several days. Yet, in the interim, the circulation may function quite adequately. Obviously, the vascular bed is able to adjust itself to an abnormal blood volume, and also a balance between capillary pressure and colloidal osmotic pressure may occur at abnormal levels. Ultimately the normal condition is restored, with a normal plasma volume and a normal concentration of protein. The exact mechanism of this return to the normal state, with the regulation of the quantity of plasma proteins, as well as their concentration, that such a return implies, remains obscure.

A third axiom, which we also owe to Starling, is the law of the heart, namely, that the force of its contraction varies with the degree of diastolic filling. He utilized this law and his hypothesis of fluid balance to explain not only the venous engorgement of cardiac failure, but also the increase in blood volume that accompanies it. He visualized then (1909) a regulation so arranged that, although the blood volume would normally vary rapidly through a small range, it might under abnormal conditions show considerable and lasting changes.

There appear, therefore, to be two conditions under which blood volume varies, namely (1), a primary change in the blood to which the size of the vascular bed is adjusted, and (2) a primary change in the vascular bed to which the blood volume is adjusted.

Turning from these axiomatic principles to a consideration of established clinical conditions, let us try to group such clinical states into these two types. Primary changes in blood volume include reductions caused by hemorrhage,<sup>5</sup> dehydration (including that secondary to artificial pyrexia),<sup>6</sup> surgical shock,<sup>7</sup> and anemia.<sup>8, 9</sup> Primary increases in blood volume include the plethoric conditions which are generated by venous infusion or blood transfusion,<sup>1, 10</sup> and probably polycythemia vera.<sup>9</sup> Primary changes in the vascular bed which lead to increases in blood volume occur with symptomatic polycythemia, cardiac disease, congestive heart failure,<sup>11</sup> and hyperthyroidism.<sup>12</sup> Primary decreases in the vascular bed which lead to similar changes in blood volume are less well known, but one such condition is myxedema.<sup>12</sup>

The changes in blood volume in these clinical conditions may be very large. Reductions of blood volume caused by dehydration can amount to 18 per cent; increases in blood volume with congestive heart failure, according to Gibson and Evans,<sup>11</sup> average 40 per cent, and may attain 141 per cent. Similar increases may occur in polycythemia vera.<sup>9</sup> In contrast with these enormous variations, temporary alterations in blood volume produced by acute changes in environmental temperature,<sup>13</sup> eating, change of posture, and the like, appear rarely to exceed 10 to 15

per cent. They might, therefore, be regarded as of no clinical importance. Such a deduction would be unwarranted. The proverb that it is the last straw that breaks the camel's back is peculiarly applicable to medicine. The contrast between the effects of mild exercise on the normal subject and on the seriously ill patient exemplifies this. Such minor adjustments may, therefore, be important in upsetting balances which are temporarily in a precarious situation.

If subjects be exposed continuously to environmental temperatures near the extremes which are tolerable without either hyperpyrexia or violent shivering, much larger changes in blood volume may develop. In my laboratory,<sup>14-16</sup> changes have been observed which sometimes appear to exceed 20, or even 40, per cent. I propose to describe some of these, for I believe that these changes, and those in the cardiovascular system that accompany them, are concerned with climatic effects on the incidence of cardiovascular disease. Petersen<sup>17</sup> has performed a service to medicine in redirecting attention to the marked effect of climate on disease. His statistical data are convincing, however much one may differ with his analysis. May I draw your attention to a single one of his curves. This relates to the incidence of cerebral hemorrhage in Chicago, in 1932. The incidence was minimal in the warm months of the summer, and maximal in the spring. There was a sharp increase in the incidence in the early cool weather of the fall.

A similar effect of rapidly changing temperatures was demonstrated by the number of monthly admissions of hypertensive patients with circulatory failure in Philadelphia, as analyzed by Dr. L. B. Laplace.<sup>18</sup> You may well criticize the unwarranted implication that these seasonal effects are in any way correlated with alterations in blood volume. Admittedly, this implication is pure conjecture. The seasonal exacerbations might depend on the respiratory infections which are common in the spring and fall. However, some evidence, although it is very indirect, may be adduced to show that seasonal changes in blood volume are concerned. Changes in blood volume are likely to be associated with changes in plasma protein concentration. Data in the literature<sup>19</sup> give some indication that there are seasonal variations in this protein concentration, although I have been unable to find any statistical study on man. Such a study, however, has recently been made on horses by Dr. A. H. Craig and Dr. J. D. Gadd,<sup>20\*</sup> of the Veterinary School of the University of Pennsylvania. They have kindly allowed me to reproduce the unpublished curve of their results, which is shown in Fig. 1, for comparison with an inverted curve of the incidence of circulatory failure in hypertensive subjects (Dr. L. B. Laplace's data). There is an obvious similarity between the two curves, although they relate to different species (both sweating animals), different localities, and different years. The data suggest that the climatic changes which induce circulatory

\*To appear soon in the American Journal of Veterinary Science.

failure in patients with cardiovascular disease also induce, in horses, changes which are likely to be associated with altered blood volumes.

In considering problems dealing with blood volume, it is necessary, first, to turn our attention to the relative importance of different sections of the vascular bed in accommodating the blood. My predecessor in this lectureship, Dr. C. K. Drinker, drew your attention to the careful analysis of the vessels of the dog's stomach which was made by Mall. I, in my turn, wish to draw your attention to the quantitative study of the vascular bed in the intestine of the dog, also made by Mall, and analyzed by Schleier.<sup>21</sup> Mall ascertained the diameter and number of the various branches of the mesenteric artery. From these data I have calculated the volume of blood contained in the various segments of this system. The figures are given in Table I. It will be seen that 73 per cent of the blood in the splanchnic system can be contained in the venules and veins, and 46 per cent in the larger veins themselves. The importance of the muscular coat of the veins thus becomes clearer, for it must be able to modify the reservoir function of these vessels. Whether the same proportional capacities exist in other parts of the vascular bed is uncertain, but even superficial examination demonstrates that a large amount of blood may be contained in the venous system.

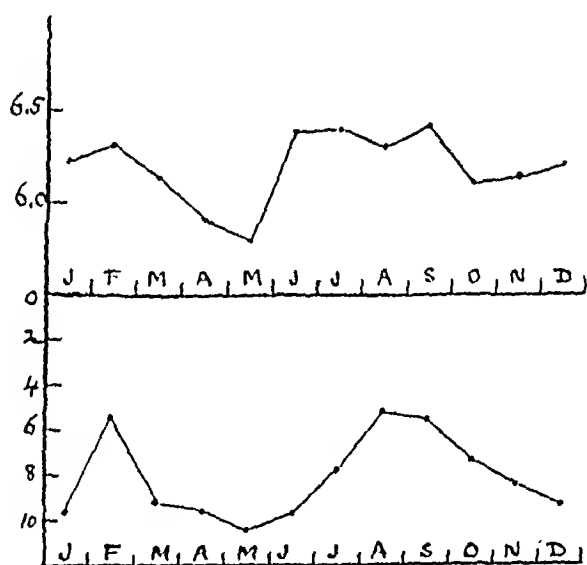


Fig. 1.—The monthly average plasma protein concentrations (Gm. per 100 ml.) in horses (data of Craige and Gadd) are plotted above, and the number of monthly admissions of hypertensive patients with cardiovascular failure to the Philadelphia General Hospital in another year (Laplace's data) below. The latter curve is plotted inverted.

The importance of veins as blood reservoirs was recognized by Starling, as well as the necessity of having an adequate pressure in the venous system in order to obtain adequate filling of the heart. Bearing in mind his principles, we may re-examine the more exact data which are now available, in order to ascertain the type of control involved. We may select experimental plethora, hemorrhage, and dehydration during pyrexia as examples of the effects of *primary changes in blood volume*,

TABLE I

MESENTERIC BLOOD VESSELS IN DOGS (OF 6 TO 7 KG. WEIGHT)  
CALCULATED FROM MALL'S DATA, AS ANALYZED BY SCHLEIER

TYPE			NUMBER	DIAMETER (CM.)	VOLUME OF CONTENTS (ML.)	TOTAL VOLUME (ML.)
a	Larger arteries	Mesenteric artery Main branches End branches	1 15 45	0.30 0.10 0.06	0.42 0.54 0.51	1.47 (8.7% of whole)
b	Smaller arteries	Intestinal branches Last branches Branches to villi Arteries of villi	1,899 26,640 328,500 1,051,000	0.014 0.005 0.0031 0.0024	0.28 0.63 0.37 0.84	2.12 (12.6% of whole)
						Total all arteries 3.59 (21.3%)
e	Capillaries	Capillaries of villi	47,300,000	0.0008	0.95	Total of capillaries, 0.95 (5.6% of whole)
d	Venules	Veins at base of villi	2,102,400	0.0026	1.16	1.16 (6.9% of whole)
e	Small veins	Veins before sub- mucosa Last branches sub- mucosa Last branches in- testinal Intestinal veins	131,400 18,000 28,800 1,899	0.0075 0.013 0.0064 0.028	0.58 0.36 1.23 1.19	3.36 (19.9% of whole)
f	Larger veins	Last branches mesenteric Branches mesenteric Mesenteric vein	45 15 1	0.15 0.24 0.30	3.09 3.01 1.68	7.78 (46.3% of whole)
						Total all veins and venules, 12.30 (73.1% of whole)

and the large increase that accompanies cardiac failure as an example of *primary change in the vascular bed*. Three of these were carefully analyzed by Starling. We may then examine the probable effects of seasonal changes in blood volume.

A primary increase in blood volume produced by the injection of defibrinated blood into a dog was carefully studied by Starling. His classical description may be followed, for little can be added to it. Although transfusions in man involve the same principles, they are not normally given rapidly enough, or in sufficient quantity, to produce any marked changes.<sup>10</sup> Starling<sup>1</sup> described his experiments as follows: "The injection increases the filling of the heart. . . . On this account the arterial pressure rises. A rise in arterial pressure brings about a reflex dilatation of the arterioles and therefore a difference in the distribution of pressure within the vascular system. The venous pressure rises and the

greater quantity of the injected fluid is accommodated in the big veins. There is, as the result of the rise of capillary pressures, an increased leakage of the fluid constituents of blood plasma. Evidence of this leakage is afforded by an examination of the blood a quarter of an hour after the injection. The haemoglobin content is found to have largely increased, showing that the greater part of the fluid of the defibrinated blood has already escaped out of the vascular system, leaving behind the blood corpuscles and a certain proportion of the proteins of the plasma. . . . The concentration of the blood raises the viscosity of this fluid and therefore the resistance to its flow through the capillaries. If the injection be very large, the resistance may prove too much for the heart; the systolic volume of this organ becomes larger and larger, so that more blood accumulates behind it in the big veins. . . . Finally, the over-dilated heart is unable to effect any onward movement of the blood at all, and the animal dies. Bleeding the animal brings about a rapid restoration of the heart's functions." Therefore, he thought that the increased volume is partly reduced by filtration into the tissues, but is accommodated mainly by an increased capacity of the vascular bed, caused by dilatation, active or passive, of arterioles and veins. The increased volume may cause a rise in blood pressure.

The compensating factors which counteract a reduction of blood volume caused by hemorrhage involve the opposite reactions of constriction of the arterioles and veins. They are well demonstrated by the data of Meek and Eyster.<sup>22</sup> Figs. 2 and 3 present some of their data, re-plotted. The results obtained on an unanesthetized dog are shown in Fig. 2, and, on an etherized dog, in Fig. 3. The capacity to adapt is much lowered by ether. Under ether, a loss of 8 Gm. per kilogram of body weight produced profound effects which even 28 Gm. per kilogram failed to induce in an unanesthetized animal. The anesthetic presumably depressed reflex control, besides affecting the permeability of vascular membranes. In both anesthetized and unanesthetized animals, small, rapid hemorrhages (amounting in unanesthetized dogs to 2.1 per cent of the body weight) resulted in little or no change in pulse rate or cardiac output. Adjustment appeared to be attained partly by a partial recovery of normal blood volume by the absorption of fluid, and partly by reduction of the vascular bed through constriction. Hemorrhages of intermediate size (20 to 30 per cent of the body weight in the unanesthetized dog) still produced little change in pulse rate and only a slight reduction in venous pressure and cardiac output; the arterial pressure was actually raised, and marked constriction of superficial capillaries and venules was noted. Measurements of hemoglobin concentration indicated that the replacement of blood loss by fluid absorption was slight. Carotid sinus regulation of pressure levels is inadequate to explain the rise in arterial pressure. In the earlier stages, vasoconstriction, so induced, or brought about by inadequate venous filling (Meadowall reflex), is able to maintain both circulation rate and blood pres-

sure levels close to their normal values; in these earlier stages, contraction of large veins is probably an important factor. In this later, more critical stage of repeated hemorrhage, the rise of arterial pressure appears to be the result of a last desperate effort to maintain an adequate venous return. It probably depends on marked constriction of arterioles, not for its value in increasing resistance, but in order that the blood so liberated may be utilized to maintain venous distention.

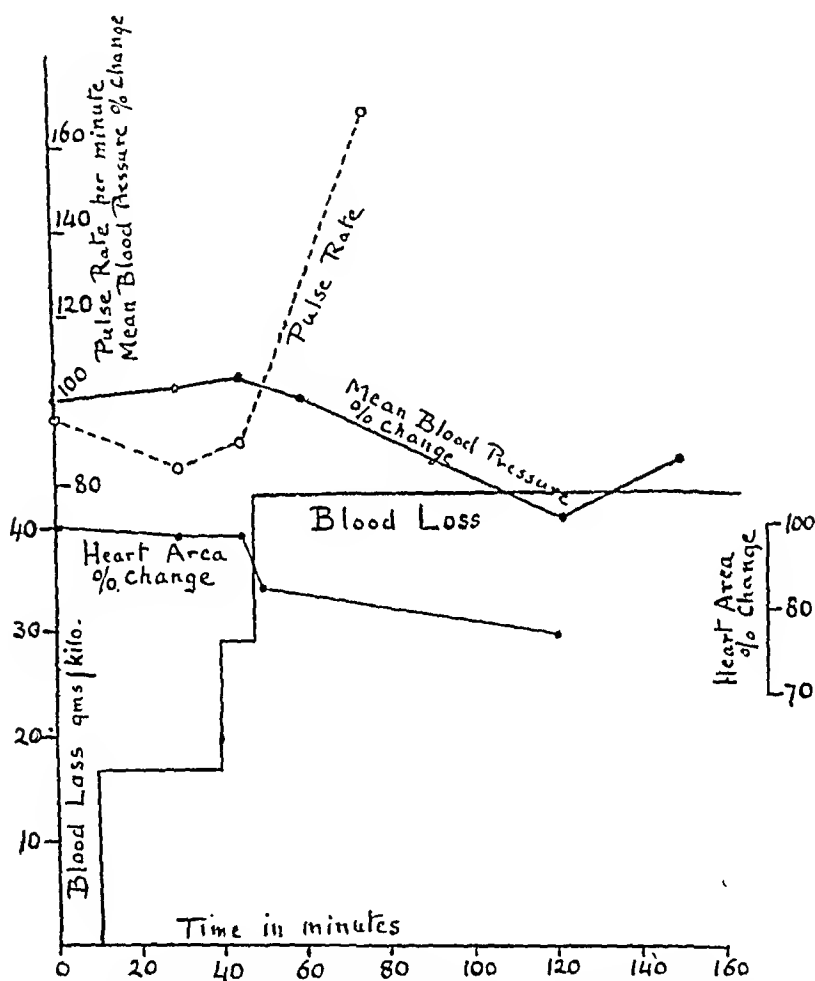


Fig. 2.—Plot representing data from a hemorrhage experiment on an unanesthetized dog (Meek and Eyster, experiment 10). The percentage change in mean blood pressure, absolute level of pulse rate, percentage change in the area of the heart's shadow, as ascertained roentgenologically, and the blood loss in grams per kilogram of body weight are shown as ordinates, with time, in minutes, as abscissae.

This would mean that arteriolar control was being used for its reservoir effect. It may, perhaps, be induced through a depressed circulation to receptors of the carotid body type, or from receptors affected by lack of distention in the veins. A decrease in blood volume may cause a rise in blood pressure.

In favor of the idea that such a constriction of arterioles may have a reservoir effect are the data obtained during pyrexia and dehydration.

Fig. 4 represents an experiment on my collaborator, Dr. J. C. Scott.<sup>23</sup> Dehydration amounting to 3.1 per cent of his body weight induced symptoms comparable with those of the critical stage of hemorrhage, for the reduction in blood volume was combined with a vascular dilatation in the skin resulting from the pyrexial conditions. The pulse rate was mounting rapidly, and this change was associated with an increase in arterial pressure. Cardiac filling was inadequate, for the basal stroke volume of 71.5 c.c. had been reduced to 38.5 c.c. The cardiac output

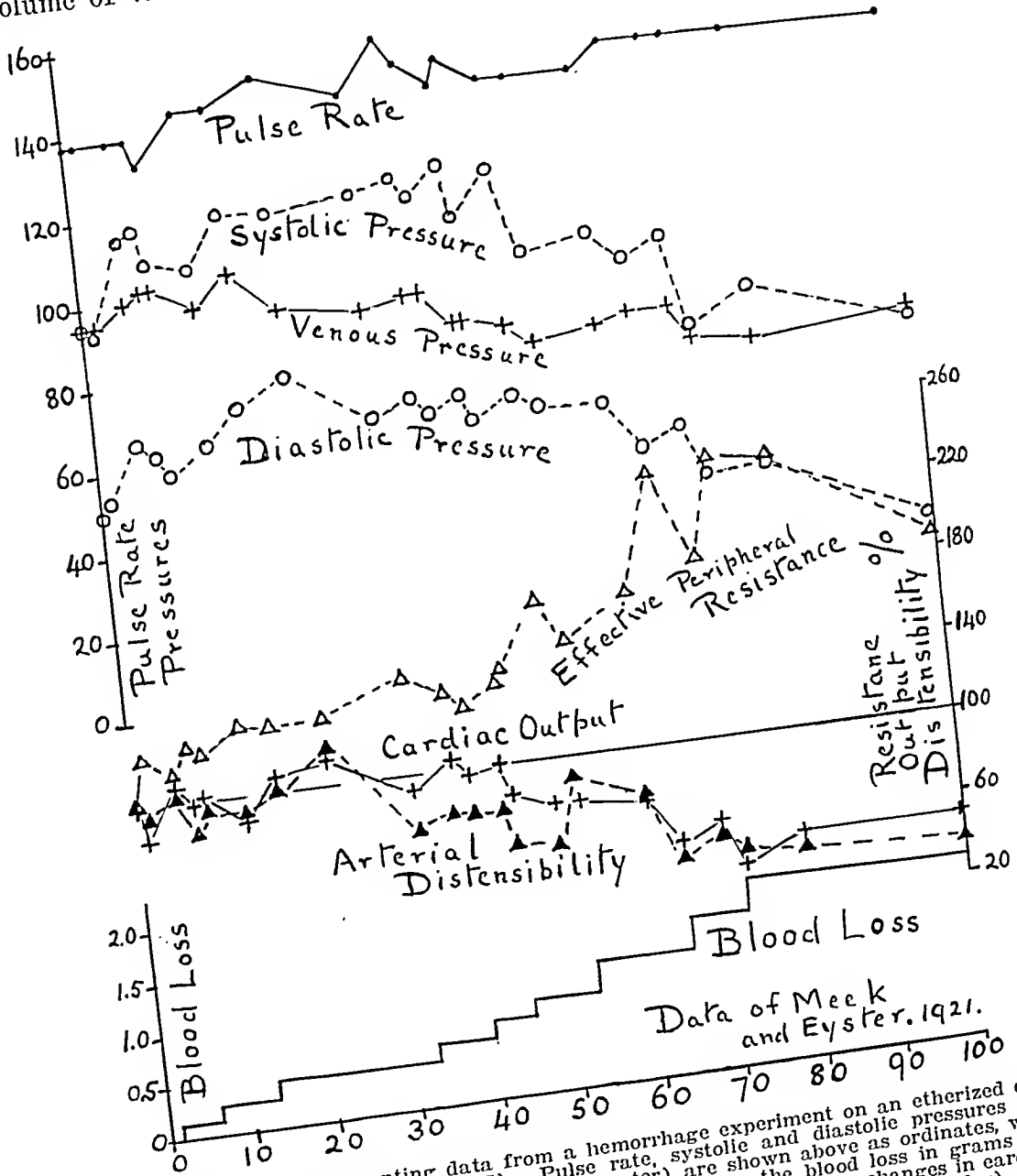


Fig. 3.—Plot representing data from a hemorrhage experiment on an etherized dog (Meek and Eyster, experiment 7). Pulse rate, systolic and diastolic pressures (in mm. Hg), and venous pressure (in mm. of water) are shown above as ordinates, with time, in minutes, as abscissae. The lowest graph shows the blood loss in grams per kilogram of body weight. In the intermediate curves the percentage changes in cardiac output per minute (crosses), the effective peripheral resistance (open triangles), and arterial distensibility (solid triangles) are shown. The resistance was estimated from the ratio of mean pressure to cardiac output, and the distensibility from that of pulse pressure to stroke volume. Evidence of constriction of both large arteries and arterioles accompanies the initial rise in arterial pressure.

was normal for basal conditions, but very subnormal for such a pyrexial condition. The subject felt extreme prostration, and showed the reflex restlessness that accompanies inadequate venous return (as after hemorrhage). Analysis showed that there was a quite marked increase in the average arteriolar constriction (increased effective peripheral resistance), despite the vasodilatation in the skin. Here again, therefore, the commencing failure of venous return was combatted, not only by muscular movements which would act as a pump, but also by pronounced

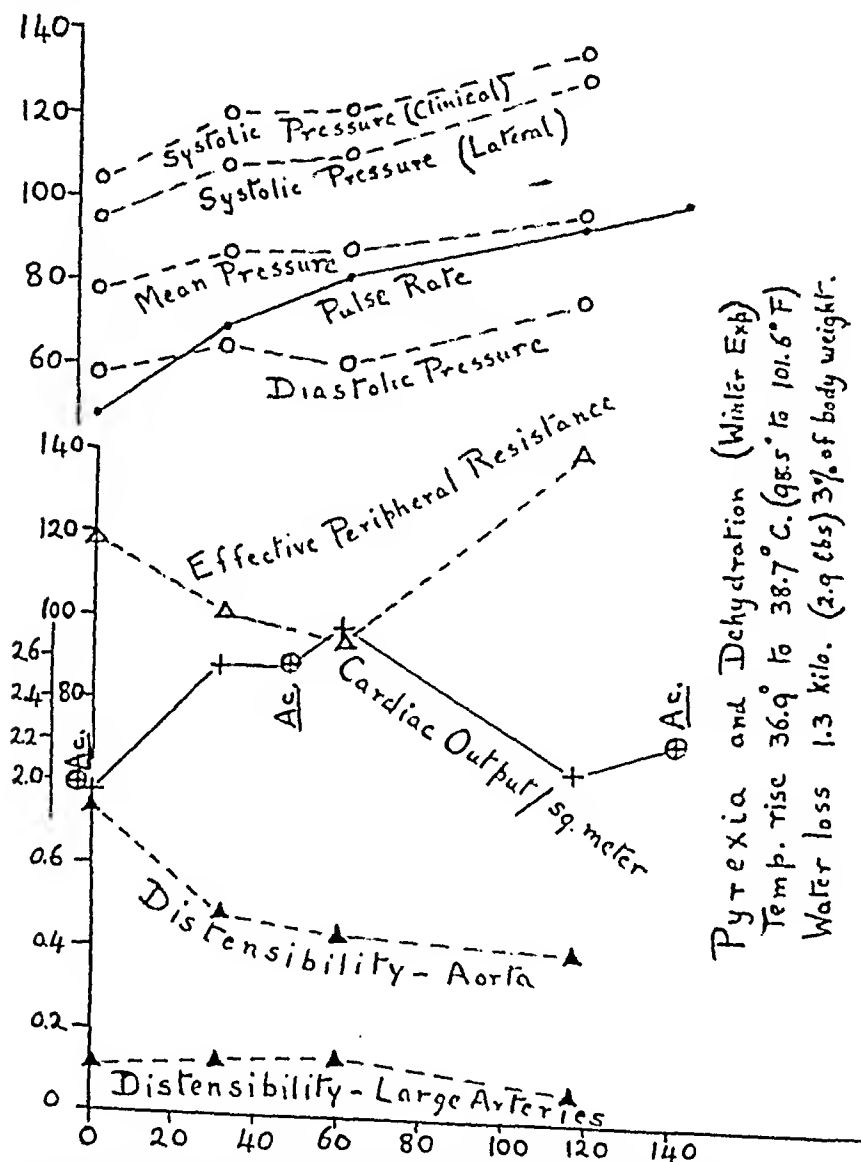


Fig. 4.—Data from a pyrexial experiment, with dehydration, in man (hot bath). The estimates of systolic, mean, and diastolic pressures (mm. Hg), of pulse rate, calculated effective peripheral resistance, cardiac output per minute per square meter of body surface, and distensibility of the aorta and of other large arteries are shown as ordinates from above downward, with time, in minutes, as abscissae. Cardiac output was estimated by the acetylene method (Ac.), or from pulse pressure and distensibility. The distensibilities were estimated from pulse wave velocities, and are expressed millimeter of mercury increase in pressure.



arteriolar constriction in areas other than the skin. The rise in arterial pressure appeared to be an index of considerable strain on the system.

It is also well established that a variation of blood volume may be produced secondarily by a primary change in the vascular bed. A simple experimental example is the increase in blood volume which results from the reduction of vascular tone caused by sympathectomy, as described by Dr. W. B. Cannon in the first of these lectures.<sup>24</sup> The enlargement of blood volume in hyperthyroidism is presumably also dependent on the general, persistent vasodilatation in both the muscles and the skin that must accompany the high metabolic rate. It is illogical to expect the organism to provide the necessary blood by persistent vasoconstriction in other areas. The mechanisms of control would presumably be the same as those involved in regeneration of blood following hemorrhage. The great increase in blood volume which is associated with cardiac decompensation is probably also secondary to the vascular conditions. It is so important that it deserves detailed attention. Probably Starling's hypothesis is at least partly correct, for he predicted that this increase in volume must develop, even before it was actually demonstrated by Lorrain Smith and McKisack,<sup>25</sup> in 1902.

Starling<sup>1</sup> described the origin as follows: "Any failure of the pump ought to tend to equalisation of pressure on the two sides of the system, i.e., to a fall of arterial and a rise of venous pressure. . . . Why is it that in cases of heart disease we find a normal arterial pressure? . . . The maintenance of an adequate output involves a continuance of high venous pressure, which can only be secured simultaneously with the maintenance of a normal arterial pressure by universal vasoconstriction. The condition, indeed, is analogous in the arteries and capillaries to that produced by bleeding, although in the case of heart failure the vascular system is bled into the veins. . . . Lowering of capillary pressure causes increased absorption. . . . The total volume of circulating fluid must be increased. . . . Chronic cyanosis must have the same effect as chronic exposure to an atmosphere of low oxygen tension, a direct excitation of the function of the bone marrow. As a result, a condition of real plethora is set up; and the vascular system contains an excess of blood of normal concentration and composition."

Modern work has amply confirmed Starling's prediction; the increase in blood volume can be very large.<sup>11</sup> The increase of cell volume somewhat exceeds that of the plasma,<sup>11, 25</sup> but, for the most part, the composition is normal, as Starling predicted. Serum protein concentrations are normal.<sup>26</sup> Starling regarded the blood volume increase as a compensation, and compared the changes to the effect of a hemorrhage into the individual's own veins. The clinician will be struck, however, with the similarity between Starling's description of plethora and the condition of the failing heart. The obvious improvement in such cases after venesection is hard to explain as the result of a compensatory increase in blood volume. There remains, therefore, a dilemma.

The changes in blood volume that may be observed in subjects who are exposed to variations in climatic conditions are probably also secondary to changes in the vascular system. If cardiac failure is accompanied by large changes in blood volume, these effects of climate may be presumed either to add to, or to detract from, the load. They must, therefore, be considered on the same hypotheses.

An increase in blood volume on exposure of normal subjects to tropical conditions was first described by Barcroft, et al., in 1922.<sup>27</sup> We have found similar changes in subjects who were exposed to warm or cool room conditions continuously for periods of four to seven days.<sup>14</sup> It is not certain that they are permanent, but they last for days. A difficulty arises in that the changes we observe commonly exceed 20 per cent, and may be as great as 40 per cent; on the other hand, Dr. W. H. Forbes<sup>28</sup> has only been able to find changes of a much smaller magnitude in subjects who were examined in Boston and Mississippi. I am indebted to him for permission to quote this personal communication. With this discrepancy in mind, Miss M. E. Maxfield, Dr. J. C. Scott, and I made measurements on four students over a period of two months in Philadelphia during the present spring. With the fairly sudden onset of spring weather, all showed an increase in blood volume. The increases averaged 19.9 per cent (maximum, 33.6 per cent; minimum, 8.9 per cent). There can be little doubt that a considerable increase in volume may occur in the spring, for a temporary fall in hematocrit reading, hemoglobin percentage, and concentration of serum protein was observed in all four subjects. The functional value of this change and the mechanisms by which it is probably brought about must, therefore, be considered. In considering these climatic effects and their probable relationship to cardiovascular disease, let us, in order to simplify the presentation, pass frankly into the borderland between fact and fancy. We can then attempt to formulate hypotheses to explain our observations. In so doing we must always remember that we are dealing partly with fancy. We must, therefore, set out to devise new observations to test our hypotheses further, and try to prevent the development of an unwarranted sense of security, a failing which has been of late so sadly prevalent in many fields.

In response to warmth there is a sequence of changes. Acute warmth produces an initial vasodilatation in the skin, with enlargement of the superficial veins, some dilution of the blood secondary to lowered capillary pressure, and a fall of blood pressure. If the warmth is near the limit for adaptation to acute changes, marked dilatation of skin vessels is possible only when a really extensive vasoconstriction in other areas makes blood available for the skin. The person has, in Starling's imagery, bled into his skin capillaries, venules, and large veins. The

\*These data have recently been published: Forbes, W. H., Dill, D. B., and Hall, F. G.: The Effect of Climate Upon the Volumes of Blood and of Tissue Fluid in Man, *Am. J. Physiol.* 130: 739, 1940.

reduction in the size of the more central vascular bed which is thus rendered necessary implies constriction of the arterioles in the central organs for a reservoir effect, so that the blood pressure is increased as it is after a moderate hemorrhage. Lowered capillary pressure increases the absorption of fluid. The lowered concentration of plasma protein causes plasma protein formation. We may imagine some reversible process, probably in the liver, which generates protein until the normal concentration in the plasma is reached. In the vasoconstriction the blood vessels supplying the bone marrow are concerned, so that this tissue, deprived of a normal supply of oxygen, is stimulated to increased production of cells. This, however, proceeds much more slowly. Once the blood volume has been increased, the necessity for central arteriolar constriction is removed, and the blood pressure returns to normal.

In response to warmth there is, therefore, an initial reduction in both plasma protein and erythrocyte concentration, with a more rapid return to normal protein, than to normal cell, concentration. The full change in blood volume does not develop until the plasma proteins have been increased in quantity, nor does it reach its full effectiveness until the cells have been proportionately increased. Since slow adjustments in metabolism<sup>15</sup> may play a role in climatic adaptation, the demands for skin dilatation, and the increased blood volume thus made necessary, may ultimately be less than in intermediate stages. The cardiovascular adjustments during this process of adaptation are much modified by the blood changes. In the early stages circulatory efficiency is poor; the pulse rate accelerates unduly on standing, and poor venous return is responsible for a very small standing stroke volume. With increased blood volume, venous return is improved; the standing pulse rate is much slower and the stroke volume greater.<sup>16</sup> Whether these circulatory changes depend on those in blood volume is less certain. Under the controlled conditions of experiments in an air-conditioned room they seem to be related; with less well-controlled conditions, such as those already mentioned in connection with the experiments on students during the spring, such relationships have so far been indefinite. It seems necessary to have the increase in blood volume before increased circulation in the fingers or dilatation of superficial veins can be utilized to the full for the maintenance of heat balance.<sup>16</sup>

The sequence of adaptation to cold is the opposite. Acute cold produces constriction of the small vessels, and also of the large veins, of the skin, with an initial rise in blood pressure and loss of fluid from the blood. If the cold is near the limit for adaptation, full skin constriction necessitates the displacement of a large volume of blood to some other area, and therefore a marked dilatation of central vessels, including the arterioles, to obtain their reservoir effect. The blood pressure, therefore, falls. Even so, a complete, generalized constriction of the skin vessels and veins is not attainable, and several days may elapse before reduction in blood volume allows this to take place.<sup>16</sup> It appears that

the body often tries to conserve plasma proteins, so that, with fluid loss from the blood, the concentration of plasma proteins may rise considerably above normal. In some persons this change may not be marked or of long duration. In all subjects the erythrocytes tend to be conserved, so that there is some rise in the hematocrit reading, and also in hemoglobin concentration. These changes must result in an increase of blood viscosity. There is (consequently?) no immediate return to a normal blood pressure level; the lowered pressures are replaced by supernormal pressures.

The occurrence of these adaptations in sequence at different rates of development makes the whole process complex. For instance, warmth induces, first, a fall of blood pressure, then a rise, and then a fall to normal or subnormal levels; cold causes, first, a rise, then a fall to subnormal levels, and then a second supernormal period before a normal level is regained. It is readily possible that the effects of warmth and cold in sequence may be additive, instead of cancelling one another, as far as blood pressure is concerned. In fact, in the early cool weather of the autumn the blood pressure is likely to be higher than in much colder weather in the spring.<sup>16</sup> May I introduce the term *consecutive adjustments, or historically determined balances*, to indicate these round-about methods of return to a normal state? The return to cool conditions following a period of warmth may be compared with the retirement of an army to defensive positions after an offence. The ground may be the same as that covered at some stage of the offence, but the position is very different. Thus, when persons are exposed, let us say, to an environmental temperature of 29° C. (84° F.), their condition depends on where they have been previously. If they have previously been adapted to cold, the blood volume is subnormal for vascular comfort, and plasma protein and erythrocyte concentrations are also subnormal. If, on the other hand, they have previously been adapted to heat, the blood volume is supernormal for comfort, plasma protein and erythrocyte concentrations are above normal, and the viscosity of the blood may be excessive.

Another factor which influences these adjustments is posture. It is well known that concentration of the blood accompanies the assumption of the erect position. Fluid is lost from the blood into the tissues, particularly in the dependent legs, with a resulting increase in the concentration of erythrocytes and plasma protein. It is not known whether the percentage change in blood volume caused by changes in posture does, or does not, vary with climatic conditions, but it is not improbable. We are certainly not justified in saying that observations made under basal conditions give us a picture of the average state of the subject, or of changes in his state.

We should not assume that either plasma protein or erythrocyte generation is likely to be uninfluenced by postural reactions, constancy of temperature conditions, and the like. In particular, night and day temperatures are likely to act somewhat differently. If new formation

of plasma proteins is continued until a certain concentration is reached, conditions at night, when the subject is lying down and blood concentrations are minimal, should be important. Such concentrations should be particularly low when the persistence of high temperatures prevents any constriction of skin vessels. There is some evidence that plasma proteins may be formed more rapidly than they are removed.<sup>14</sup> Some such sequence of events, with formation of plasma proteins particularly at night, might account for the higher concentrations of plasma protein in subjects who are exposed continuously to high temperatures,<sup>14</sup> as well as in horses during the hot summer months (Fig. 1). On the other hand, it is probable that there is, in addition, some more complex mechanism for regulation of the quantity of plasma protein, and, consequently, of plasma volume.

The increase in blood volume caused by warmth may, therefore, be regarded as very similar to that in cardiac failure. In the one case the person bleeds, as it were, into the superficial skin veins, and, in the other, into deeper, large veins. In the reaction to warmth the increase in volume is certainly a compensatory mechanism, and is accompanied by a slower pulse rate, a larger stroke volume when standing, and other evidence of greater cardiovascular fitness. There remains the dilemma that, in cardiac failure, bloodletting is so commonly of great benefit to the patient; the blood volume has apparently been too large. To explain this, one has only to assume that there is a constant reaction to chronic circulatory failure, in which peripheral vasoconstriction and increased erythrocyte formation, together, bring about greater venous filling, with stretching of the heart muscle in diastole. This reaction would then proceed to raise the venous pressure when cardiac output decreased, regardless of whether the venous pressure was rising towards its optimum value or had already passed it.

Reactions to temperature and posture with modifications of blood volume would then play their part. Heart failure would most commonly develop when the patient was doing light work in the erect posture. Adaptation to this work might already have been attempted by utilization of the venous engorgement mechanism to or beyond its optimum. When failure occurs, and the patient is forced into a position of partial recumbency, the blood volume is still further increased by the fall in capillary pressure in the dependent parts of the body and the consequent absorption of excess tissue fluid. Venous engorgement is thus exaggerated. This exaggeration in the recumbent position may be one of the many factors that make complete recumbency impossible for the patient with heart failure. If this series of events is complicated by a sudden change from warm to cooler weather, necessitating shunting of the skin blood to the deeper vessels, adverse conditions may be aggravated. Even in normal subjects, a change from hot to cooler weather may be associated with evidence of vascular engorgement, such as epistaxis. The abrupt changes of temperature utilized in our experi-

mental room have not given rise to symptoms in the young subjects that have been mostly employed. Symptoms might be more in evidence in older subjects. In the one older subject whom we used (who is somewhat hypotensive), the only symptoms during abrupt warming were edema of the feet, weakness, and incapacity for mental concentration, and, during abrupt cooling, palpitation on going to bed.

Abrupt changes in temperature might affect the circulation in many ways. A sudden change to warmer weather might leave the blood volume too low, and cause inadequate filling of a heart which needed a high venous pressure for effective action. Vasoconstriction, with a rise in arterial pressure and an increased load on the heart, might result. A sudden fall in temperature might make the blood volume excessive in conditions characterized by superficial vasoconstriction, and so cause venous engorgement. This seems to be a sequence which is likely to give rise to a vicious circle. High blood pressure might develop either on exposure to warmth, with an inadequate venous return, or, in the initial reaction to exposure to cold, with a relative plethora, and either might play a part in facilitating cerebral hemorrhage. Again, the low pressures that develop in the second stage of exposure to cold might be accompanied by poor coronary supply and favor coronary thrombosis. In any case, all of these reactions are likely to be not only of greater importance, but also of greater magnitude, when the cardiovascular system has been rendered inelastic by disease or old age. Increased viscosity may be of little importance in normal vessels, the lumens of which can be adjusted. It may be of immense importance in diseased vessels with small and unadjustable lumens. Clinical observation of such subjects during periods of rapidly changing temperature might do much to clarify the situation. One important factor which determines plasma volume is the quantity of plasma protein in circulation. It is, consequently, a pity that in many reports of plasma volume measurements no data are given concerning plasma or serum protein concentration.

Lastly, we have supposed that there is a constant reaction to chronic circulatory failure, in which venous engorgement plays an important role; how are we to explain its absence in some cases? As Starling stated in the passages quoted, the failure of the pump mechanism causes a rise in venous pressure, and this is true whatever the condition. However, the real picture of massive venous engorgement requires a considerable increase in blood volume, with its concomitant increase in the circulating plasma protein and erythrocytes, and these processes take time to develop. It is true that a very similar venous engorgement may develop acutely, without such an enlarged blood volume, but only by generalized arterial constriction in acute reactions that cannot be long maintained. Failure without venous engorgement can, therefore, take place when the changes are too rapid to allow the compensatory increases in blood volume to occur, and when the effects of intense vasoconstriction

are prevented by toxemia, vasomotor fatigue, increased permeability of the capillaries in shock, and the like.

Many other points should have been discussed. It is probable that some cardiovascular disabilities result from a disordered control of blood volume. Some cases of postural hypotension may belong in this class. More suitable methods for blood volume measurement are required, although this is not the time and place for a discussion of technique. I believe, however, that recent modifications of the carbon monoxide method may make it more suitable for clinical use than the dye methods, with their demand for numerous blood samples.

In conclusion, I do not feel that I need apologize for my extensive references to, and quotations from, that grand old master of physiology, Professor Starling. I can only regret that he is not still alive to analyze these newer data with the consummate skill which he used for the older, and that I myself have not been in the audience listening to him.

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# ROENTGENOLOGIC STUDIES OF THE SIZE OF THE HEART IN CHILDHOOD

## I. THREE DIFFERENT TYPES OF TELEROENTGENOGRAPHIC CHANGES WHICH OCCUR IN ACUTE RHEUMATIC FEVER

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### INTRODUCTION

**I**N A PREVIOUS paper,<sup>1</sup> evidence was adduced to show that in rheumatic heart disease the size of the heart depends not primarily upon the severity of the valvular lesion, but upon the extent of the myocardial damage. The author cited one case in which the heart appeared to be within normal limits four years after the development of mitral and aortic insufficiency and stenosis. In two other cases, notwithstanding valvular damage, the size of the heart had remained stationary over a period of years. Finally, there was the case of a child whose heart had been enormous at the age of 5 years, but seven years later was within normal limits. In the latter case, superimposition of the teleroentgenograms which had been taken at yearly intervals showed that the change in the size of the heart was a relative one, i.e., the heart had remained constant in size and the chest had grown.

How great is the significance of these observations depends upon a number of factors, such as the centering and target-film distance, the phase of the cardiac cycle, and the phase of respiration. Each of these factors is subject to minor variations. Nevertheless, when six successive roentgenograms, taken at yearly intervals, show that the heart is always of the same size and contour, it is improbable that this uniformity is the result of a summation of chance variations. Certainly chance cannot be a factor if similar findings occur in a number of different cases.

In the paper just referred to, the cases were cited as examples of phenomena which have been observed in acute rheumatic fever. The purpose of the present investigation was to study the changes in the size of the heart, as ascertained by means of teleroentgenograms, in a large series of cases of rheumatic heart disease. As a result of the study, we have been able to differentiate three definite and distinct sequences of changes in the size of the heart. In one group of cases, in spite of valvular lesions, the size of the heart remained within normal limits, and its increase in size was that of normal growth; in the second group

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of cases the heart, after it enlarged, remained stationary in size while the chest grew; in the third group there was progressive cardiac enlargement. The purpose of this paper is to present these observations and to compare briefly the clinical course of the disease in the several groups.

#### MATERIAL AND METHOD

The study is based upon routine teleroentgenograms, taken on patients who were being cared for in the cardiac clinic. Inevitably, in many instances, we failed to obtain teleroentgenograms as frequently as, in retrospect, would have been desirable. Further, not all of the roentgenograms were satisfactory. In some the patient was rotated; in others the exposure was made at the end of extreme inspiration or expiration. A few were open to question because of doubt concerning the target-film distance. All such roentgenograms were discarded.

Changes in the size of the cardiac shadow caused by pericardial effusion were not included. In every case in which this was suspected, teleroentgenograms suggestive of effusion were excluded. We, of course, included not only the cases of chronic valvular disease, but also those of acute myocarditis.

Our method of study was similar to that used by Palmer,<sup>2</sup> namely, the changes in the size of the heart were studied by the superimposition of one teleroentgenogram upon another. Palmer's studies were made on adults; he considered that changes in the size of the heart were significant only if the size of the chest remained constant. Inasmuch as we studied children, such criteria were not possible; it was essential to take into consideration the factor of growth.

The cardi thoracic ratio offers the simplest means of comparing the rate of growth of the heart and the chest. We appreciate fully that this method is not an exact one; nevertheless, speaking in broad terms, it does give an indication of the relative size of the heart and chest.

In addition, we attempted to compare the size of the heart with the theoretically normal size for persons of the same age, height, and weight. This method, too, is not accurate, for none of the studies on normal subjects include persons from 5 to 20 years of age.

For children between the ages of 4 and 16 years, we used the standards established by Ziskin.<sup>3</sup> He correlated the transverse diameters of the heart and the chest with height and age. Whenever possible, we correlated the size of the heart with height. In the few instances in which the height was not recorded, we had to correlate the size of the heart with the age\* of the child. For children over 16 years of age we used the normal standards of Ungerleider and Clark.<sup>4</sup>

Ungerleider and Clark's standards start with the age of 15 years, a weight of 83 pounds, and a height of 60 inches. These investigators believe that after the age of 15 years the size of the heart varies not with age, but with height and weight. The majority of children reach 60 inches in height and 83 pounds in weight in early adolescence. Therefore, in all instances in which our children had attained this height and weight, we used both standards, i.e., those of Ziskin and those of Ungerleider and Clark.†

\*In such cases we also compared the transverse diameter of the chest with the normal for the age, in order to ascertain whether or not the child was of normal size for his age.

†Our group of supposedly normal subjects, i.e., those with a normal cardi thoracic ratio who were of average height and weight for their age, fell within the limits of normal for both sets of standards. There were seventeen children whose growth we had classified as normal who were over 60 inches in height and weighed more than 83 pounds. A comparison between the size of the heart in these cases with that given by Ungerleider and Clark showed that fifteen of the seventeen subjects fell within 5 per cent of the average for the height and weight; the remaining two were within 10 per cent of the average. The latter percentage of variation is at the present time regarded by Ungerleider and Clark as representative of the (continued on next page)

Our studies were based on frontal planes. We have no series of measurements in the oblique or lateral views and, therefore, can make no comparative studies of enlargement in the posterior plane. Great enlargement in the posterior plane usually alters the size or contour of the heart in the frontal plane. Although this is not always true, it is admittedly a source of error. It must also be admitted that these studies make no allowance for the volume of the heart or the thickness of the muscle wall. Granted these limitations, it is generally accepted that teleroentgenograms do give useful information concerning the size of the heart.

We did not attempt specifically to measure cardiac areas, because the method of superimposition of teleroentgenograms reveals changes in cardiac area. In a few instances, although the transverse diameter of the heart did not increase, the contour of the heart changed and the tracings clearly showed a definite increase in the cardiac area. Such cases\* were not included in this study.

#### CASES IN WHICH THE HEART SHOWED NORMAL GROWTH

It is well known that there are many children who suffer from a single attack of acute rheumatic fever, and yet, in later life, show no cardiac abnormality. In addition, there are a few who suffer from multiple attacks of acute rheumatic fever without developing valvular heart disease. Some of these children never show any clinical evidence of cardiac involvement; others, during the acute stage of the disease, present slight, but definite, evidence of myocardial strain which disappears with the subsidence of the acute infection. The majority of these children do well. Their hearts remain normal. As the child grows, the heart increases in size in the normal manner. This phenomenon is familiar to all and calls for no comment. A case of this kind is presented merely to serve as a basis for comparison with those which follow.

CASE 1.—A. M. (H.L.H. No. 77466), a white girl, had had two comparatively mild attacks of rheumatic polyarthritis, each followed by chorea—the first in April, 1932, and the second in September, 1934. Throughout both attacks the child was kept at rest in bed. Each time, at the height of the rheumatic infection, although there was no demonstrable cardiac enlargement, examination of the heart revealed a soft systolic murmur which was transmitted to the axilla. After the subsidence of the rheumatic infection, all signs of cardiac strain disappeared and the girl has remained well.

The composite picture of the tracings of the teleroentgenograms is shown in Fig. 1. The various measurements are given in Table I.

\*One case (Fig. 6b) is presented merely to illustrate the case with which such cases can be differentiated from those with which we are concerned.

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(continued from preceding page) limits of normal. Therefore, we concluded that for children of average height and weight the two standards were equally reliable.

There was a wide discrepancy between these two sets of standards when they were applied to obese children. This discrepancy is, in all probability, caused by the fact that Ungerleider and Clark included in their series a large number of short, stocky, heavily built adults and allowed for an increase in the size of the heart in proportion to the weight of the subject, whereas Ziskin studied subjects under 16 years of age and made no allowance for increasing weight. We believe that, in such cases, the normal size of the heart is probably represented by a value intermediate between the two standards.

The standards of Ungerleider and Clark were also inadequate when they were applied to patients who, because of illness, had lost weight rapidly. In such cases it is not to be expected that the heart will decrease in size in proportion to the loss of body weight. Therefore, it is clear that these standards cannot be considered precise. Indeed, all comparisons between the actual size of the heart and the normal for the age, height, and weight are but rough indices. Nevertheless, broadly speaking, we believe that they are useful indices.

TABLE I

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVI- ATION FROM AV.
May, 1932	8	8.7	18.3	47.5			8.9	-3
January, 1934	10	9.6	20.0	48.0	53	70½	9.5	0
January, 1935	11	10.0	21.5	46.5	56	72½	9.65	+4
November, 1937	13	10.2	23.7	43.0	61	92½	10.5	-3

T.D., Transverse diameter; I.D., internal diameter.

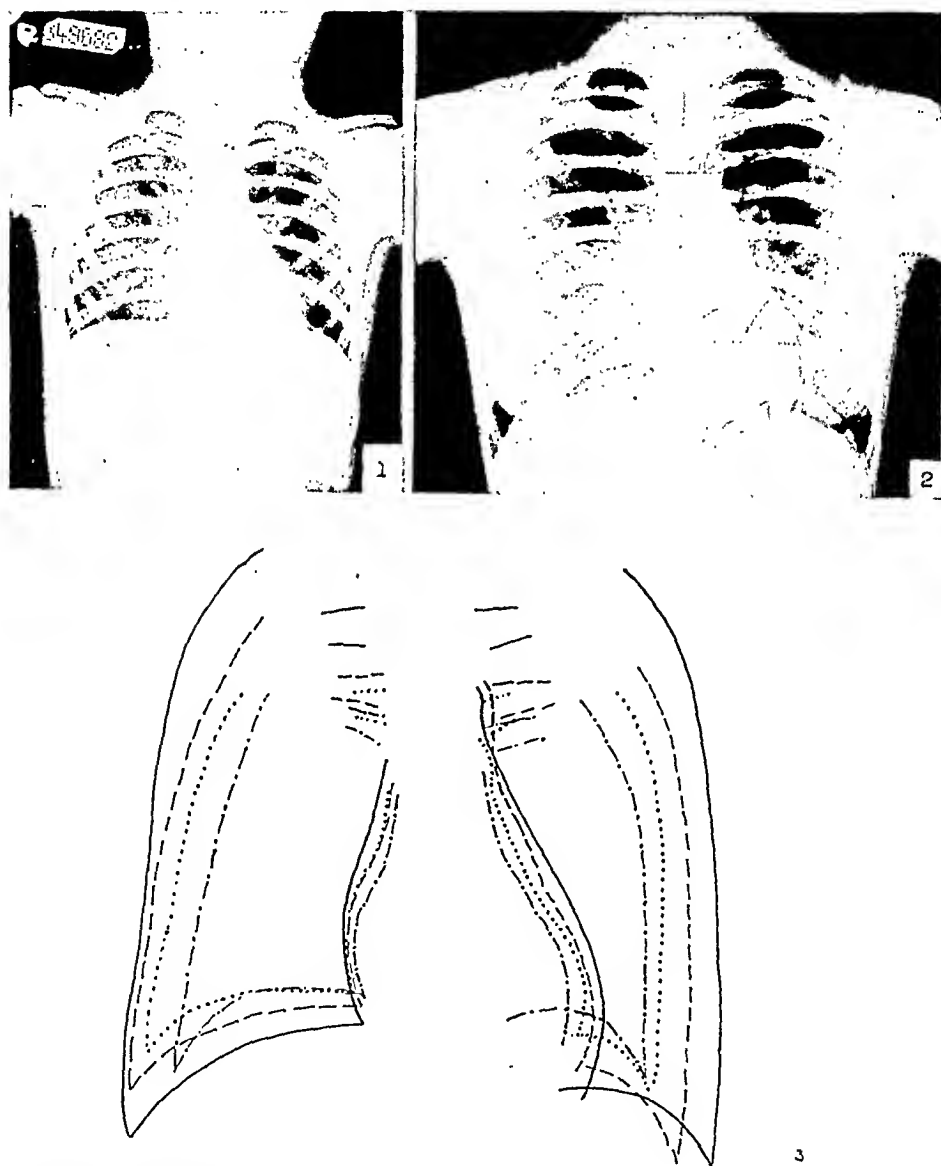


Fig. 1.—Normal growth. Case 1 (normal heart). 1, Teleroentgenogram 5/4/32. 2, Teleroentgenogram 11/10/37. 3, Tracings of teleroentgenograms 5/4/32 — . — . — ., 1/20/34 . . . . ., 1/14/35 — — — — —, 11/10/37 — — — — —.

In this case, the transverse diameter of the heart increased steadily in proportion to the growth of the chest. The cardiothoracic ratio remained relatively constant until puberty, and then decreased, as it normally does. A comparison between the actual size of the heart and the theoretical average transverse diameter for her age, height, and weight also showed that the size of the heart closely approximated the normal. In this case it was only during the attacks of rheumatic fever that there was any evidence of cardiac involvement. The heart was never enlarged, and there was no evidence of chronic valvular damage. Hence, it is not remarkable that the growth of the heart was normal.

It is, however, highly significant that the same phenomenon can occur in cases of chronic rheumatic valvular disease, as illustrated in Case 2, in which the boy had an aortic insufficiency of seven years' duration.

CASE 2.—J. G. (H.L.H. No. 26003), a negro, was born in 1920. He was first seen at the Harriet Lane Home in May, 1930, at which time he had acute arthritis. Shortly after the onset of the illness he developed signs of aortic insufficiency. He was kept in bed for eight months. In May, 1932, he had a mild recurrence of polyarthritis, associated with fatigue and dyspnea. He had another mild recurrence of acute rheumatic fever in February, 1935. Since then he has remained well. The signs of aortic insufficiency have persisted.

The composite picture of the tracings of the teleroentgenograms is shown in Fig. 2. The actual measurements of the transverse diameter of the heart and chest are given in Table II.

In this case the cardiothoracic ratio was never above 43 per cent. It is evident that the size of the heart was always within normal limits, and that the increase in its size was proportional to the growth of the chest. This case clearly illustrates that aortic insufficiency does not necessarily cause the heart to enlarge out of proportion to the normal growth of the body.

In brief, we have observed forty-four children whose hearts have never been above the upper limit of normal size in spite of the fact that they have had acute rheumatic fever. In these children the increase in the size of the heart has been essentially that of normal growth. Of these children, thirty are similar to the first patient cited. They had mild infections. In fifteen instances the outstanding rheumatic manifestation was chorea. Some suffered recurrences; two had repeated recurrences. One child had eight, and another nine, attacks of chorea. All of these children at some time showed slight evidence of cardiac involvement; none has any residual evidence of valvular damage.

There are, however, fourteen cases which are similar to the second example in that the cardiac murmurs have persisted to date; nine have mitral insufficiency; three have aortic insufficiency; and one has mitral insufficiency and a mid-diastolic murmur. During the period of observation five of these children had recurrences of acute rheumatic fever; all of them were treated with long periods of rest in bed.

TABLE II

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVI- ATION FROM AV.
October, 1930	10	9.2	21.5	42.8	55	62½	9.6	-4
March, 1932	12	9.5	22.6	42.0	59	73½	9.9	-3
November, 1934	14	10.3	24.8	41.5	64	99½	10.6	-2
February, 1936	16	10.9	26.5	41.1	67	116½	11.2	-2
January, 1938	18	10.8	27.5	39.2	68½	128½	11.7	-7

T.D., Transverse diameter; I.D., internal diameter.

Italicized figures are those given by the insurance company.

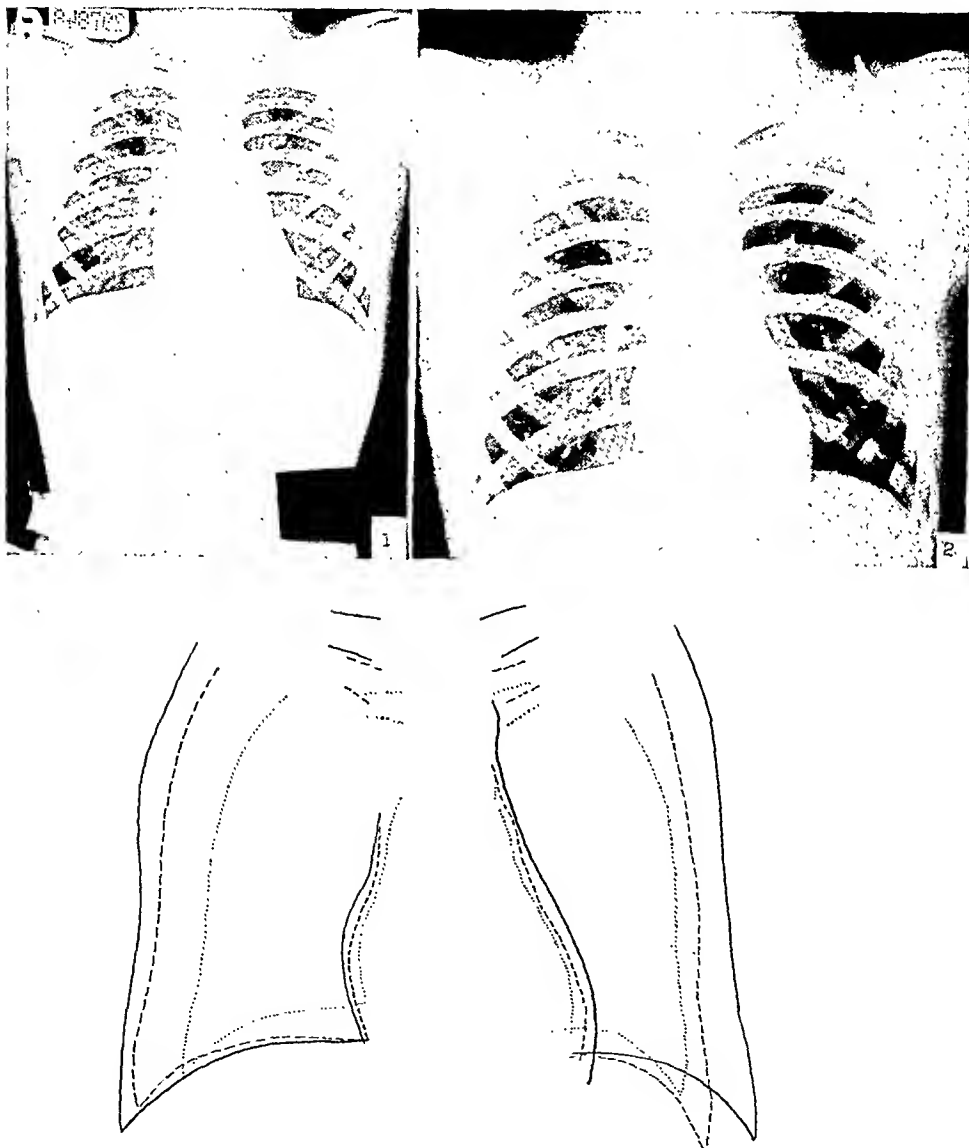


Fig. 2.—Normal growth. Case 2 (aortic insufficiency). 1, Teleroentgenogram 10/13/30. 2, Teleroentgenogram 1/27/38. 3, Tracings of teleroentgenograms 10/13/30 ..... 11/12/34 — — — — —, 1/27/38 — — — — —.



TABLE III

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVI- ATION FROM AV.
June, 1932	5	11.2	18.5	60.5		33	8.5	+30
September, 1933	6	10.9	19.6	55.6		58	8.6	+25
October, 1934	7	11.5	21.3	54.0		73	9.0	+26
April, 1936	9	10.5	23.4	44.8	58	85½	9.8	+ 7
August, 1936	9	10.5	23.4	44.8	59	84	9.9	+ 6
May, 1937	10	11.0	24.7	44.5	61	91	10.3	+ 7
December, 1938	11	10.6	24.7	42.9	61½	107½	11.2	- 5

T.D., Transverse diameter; I.D., internal diameter.

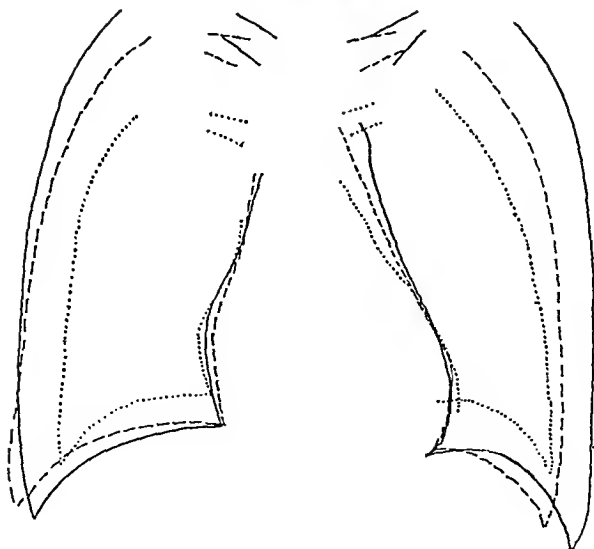


Fig. 3b.—Size of heart stationary; chest growing. Case 3 (mitral insufficiency).  
 1, Same as Plate 3a, 2, 2, Teleroentgenogram 12/3/38. 3, Tracings of teleroentgenograms  
 10/10/34 . . . . . (Same as . . . Plate 3a, 3), 8/24/36 — — — — —, 12/3/38



when the patient first came under observation; thereafter, the size of the heart remained stationary while the chest grew. In a number of instances the result has been that the size of the heart eventually came to lie within normal limits. This phenomenon was new to us, and we believe that it is not generally appreciated. Therefore, a few illustrative cases are presented.

CASE 3.—D. W. (H.L.H. No. 77441), a white girl, was born in 1926. She was first brought to the Harriet Lane Home when she was 5 years of age, at which time she had a severe rheumatic infection, cardiac enlargement, tachycardia, gallop rhythm, and a pronounced mitral insufficiency. She remained in the hospital two months, and was then transferred to our convalescent home, where she remained three years, except that each summer she returned home for a short stay. This was permitted because her ultimate prognosis seemed so unfavorable. Throughout the three years she had fever and tachycardia; finally, in 1935, she was sent home to remain in bed. In May, 1936, four years after the onset, her sedimentation rate returned to normal, and she was allowed to get up gradually. In March, 1937, she had the "flu," which, in all probability, was a rheumatic exacerbation. She was put back to bed for several months. In November, 1938, she developed subacute bacterial endocarditis and died in April, 1939. At the autopsy the heart was described as "perhaps slightly enlarged."

The composite picture of the tracings of the teleroentgenograms is shown in Figs. 3a and 3b. The actual measurements of the transverse diameter of the heart and chest are given in Table III.

Figs. 3a and 3b (the dotted line in Fig. 3b, is the duplicate of the dotted line in Fig. 3a) illustrate how slight was the change in the size of the heart over the period of years. Ever since 1932, examination of the heart had shown definite signs of mitral insufficiency.

Although these teleroentgenograms show that the transverse diameter of the heart has varied slightly, on the whole it has remained remarkably constant, whereas the chest has grown steadily. During this period the child grew in stature and gained in weight. The cardiothoracic ratio fell from 60.5 to 42.9 per cent. The heart, which was originally 30 per cent larger than the theoretical normal for her age, was, at the time of her final illness, 5 per cent smaller than the average for her age, height, and weight.

In this case it is obvious that the heart did not enlarge progressively; indeed, the heart did not even increase in size in proportion to the growth of the child. On the contrary, the size of the heart remained relatively unaltered while the child grew.

CASE 4.—M. M. (H.L.H. No. 29031), a white boy, was born in 1921. He was first seen at the Harriet Lane Home in 1933. He gave the history that he had had his first attack of acute rheumatic polyarthrititis in 1929, a second in 1931, and a third in 1932. In February, 1933, he had a fourth attack of polyarthrititis. The following month he was brought to the hospital with severe pancarditis and pericardial effusion (these teleroentgenograms are not included). His heart appeared to be enlarged, and he had a systolic murmur, a mid-diastolic murmur, and gallop rhythm. He was in the hospital five weeks and was kept in bed for an additional

TABLE IV

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVI- ATION FROM AV.
March, 1933	12	12.0	24.3	49.0	55	66	9.5	+28
September, 1933	12	12.2	24.8	49.5	56	81½	9.6	+27
May, 1934	13	12.4	26.7	46.4	61½	106½	10.0	+24
							<i>11.2</i>	<i>+10</i>
July, 1936	15	12.3	28.0	43.9	63½	118½	10.4	+18
							<i>11.5</i>	<i>+ 7</i>
June, 1938	17	12.5	29.5	42.3	64½	128½	<i>12.0</i>	<i>+ 4</i>

T.D., Transverse diameter; I.D., internal diameter.

Italicized figures are those given by the insurance company.

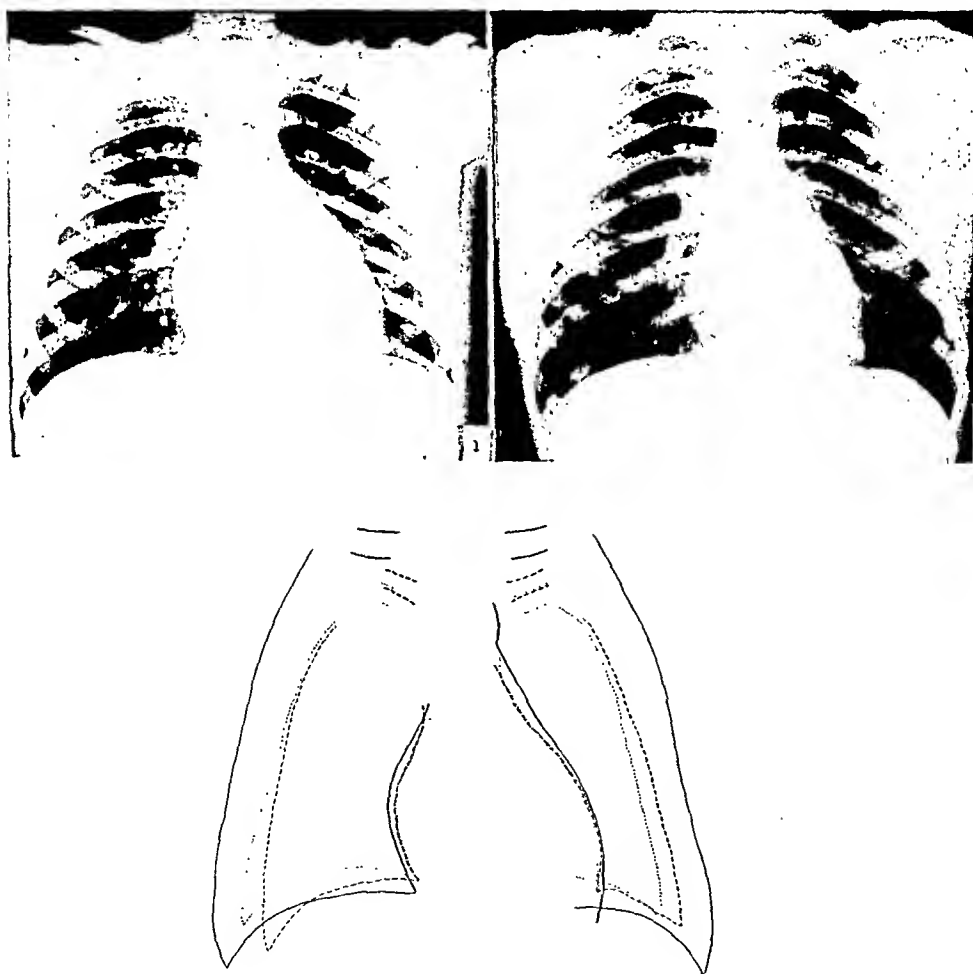


Fig. 4.—Size of heart stationary; chest growing. Case 4 (mitral insufficiency and mitral stenosis). 1, Teleroentgenogram 3/30/33. 2, Teleroentgenogram 6/24/38. 3, Tracings of teleroentgenograms 3/30/33 . . . . . 9/12/33 — — — — —, 6/24/38

three months. In October, 1933, he suffered from an exacerbation of his rheumatic infection, and was in bed one month. In July, 1934, he had his sixth attack of rheumatic polyarthritis; he was in bed four months and remained out of school throughout the year 1934-35. Since 1934 he has been well. He is now at work. His heart shows definite evidence of mitral insufficiency and stenosis.

The composite picture of the tracings of the teleroentgenograms is presented in Fig. 4. Table IV gives the actual measurements of the heart.

In this case the transverse diameter of the heart increased only 0.5 cm. over a period of five years; the internal diameter of the chest increased 5.2 cm. The cardiothoracic ratio dropped from 49 to 42.3 per cent.

CASE 5.—F. B. (H.L.H. No. 82392), a white boy, was born in 1922. He was first seen at the Harriet Lane Home in March, 1933, during his third attack of severe rheumatic polyarthritis. His first attack of rheumatic fever occurred in 1930, and his second in 1931. When brought to the dispensary he not only had polyarthritis, but also pancarditis and consolidation of the lung. On admission he had signs of pericardial effusion and pneumonia (therefore, no teleroentgenograms taken before October, 1933, are shown). He remained in the hospital two months and was in bed at home for eight months. During the spring of 1934 he was allowed to get up gradually; he finally returned to school in September, 1934. Since September, 1934, the boy has been well. He has had no recurrence. From 1931 to 1936 there was evidence of only slight mitral insufficiency; in December, 1936, he developed questionable signs of mitral stenosis. Both have persisted unaltered to date.

The composite picture of the tracings of the teleroentgenograms is presented in Fig. 5. The measurements are given in Table V.

In this case the measurements showed a maximum variation of 1.0 cm., and a difference of only 0.5 cm., between October, 1933, and December, 1938. Theoretically, the diameter of the heart should have increased 1 to 2 cm. The consequence of these changes is that, whereas, in 1933, the size of the heart was 18 per cent above the average for his age and height, in 1938 it was 12 per cent above the normal standard given by Ziskin, but only 1 per cent above that given by Ungerleider and Clark.\*

CASE 6.—T. W. (H.L.H. No. 75770), a white boy, was born in 1922. He first came to the Harriet Lane Home, in 1932, because of chronic tonsillitis; his heart was entirely normal. He was next seen in July, 1934; at that time he stated that, in 1933, he had a severe attack of rheumatic fever, and was in St. Joseph's Hospital for four months. For nine months thereafter he was kept quiet and received digitalis. When he was examined in July, 1934, his heart was enormous, and there were definite signs of mitral insufficiency and stenosis. Since then he has remained well.

The composite picture of the tracings of the teleroentgenograms is presented in Fig. 6a, and the actual measurements of the heart are given in Table VI.

Lest it be thought that the size and contour of the heart in this case were such that further enlargement would not be discernible, the

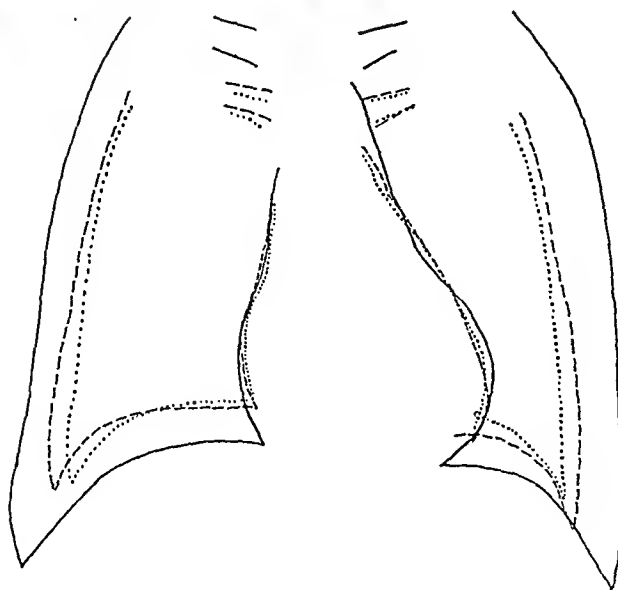
\*The boy was 68 inches tall, and of normal build. Ziskin's study did not include many children of this height. Therefore, we believe that the standards given by Ungerleider and Clark are probably more accurate than those of Ziskin.

TABLE V

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVI- ATION FROM AV.
October, 1933	11	11.4	23.4	48.7	57½	79	9.7	+18
July, 1934	12	11.8	25.7	45.9	60	88½	9.8	+20
							<i>10.3</i>	<i>+14</i>
December, 1936	14	12.4	28.8	43.1	67	122	10.6	+17
							<i>11.4</i>	<i>+9</i>
December, 1938	16	11.9	29.4	40.0	68	129	10.6	+12
							<i>11.7</i>	<i>+1</i>

T.D., Transverse diameter; I.D., internal diameter.

Italicized figures are those given by the insurance company.



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Fig. 5.—Size of heart stationary; chest growing. Case 5 (slight mitral insufficiency and questionable mitral stenosis). 1, Teleroentgenogram 10/6/33. 2, Teleroentgenogram 12/9/38. 3, Tracings of teleroentgenograms 10/6/33 . . . . ., 7/6/34 . . . . ., 12/9/38 . . . . .

TABLE VI

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVI- ATION FROM AV.
August, 1934	12	12.3	21.0	58.5	50	51½	9.6	+28
January, 1939	17	11.8	23.5	50.2	58	80	10.1	+17

T.D., Transverse diameter; I.D., internal diameter.

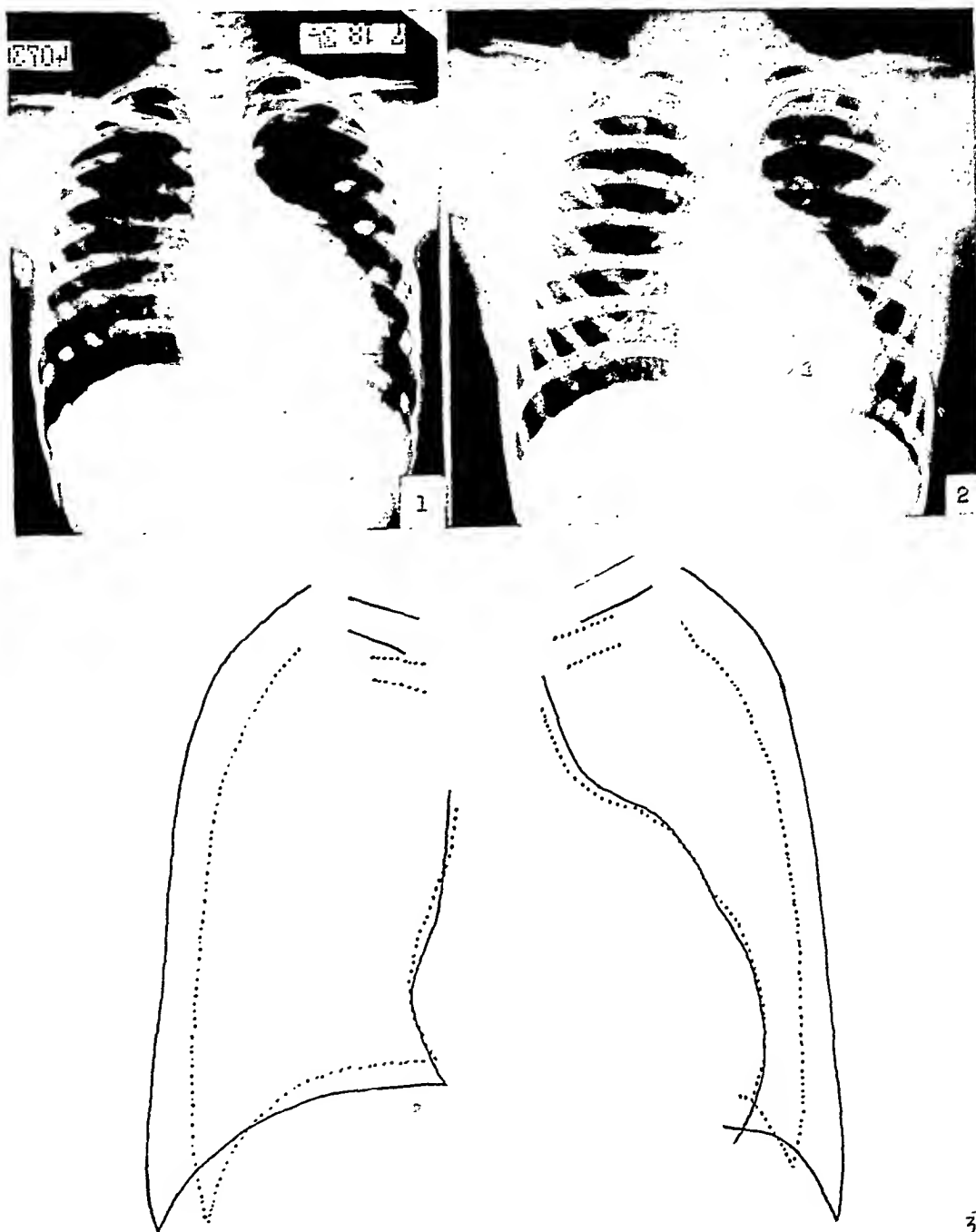


Fig. 6a.—Size of heart stationary; chest growing. Case 6 (mitral insufficiency and mitral stenosis). 1. Teleroentgenogram 7/18/34. 2. Teleroentgenogram 1/23/39. 3. Tracings of teleroentgenograms 7/18/34 . . . . . 1/23/39 ———.

teleröntgenograms of another patient with severe rheumatic infection and mitral insufficiency and stenosis are presented in Fig. 6b.

In the latter case, although the transverse diameter of the heart did not increase, it is clear that the surface area enlarged.

These cases suffice to illustrate the phenomenon. Although there was slight variation in the size of the heart, the trend is perfectly clear;

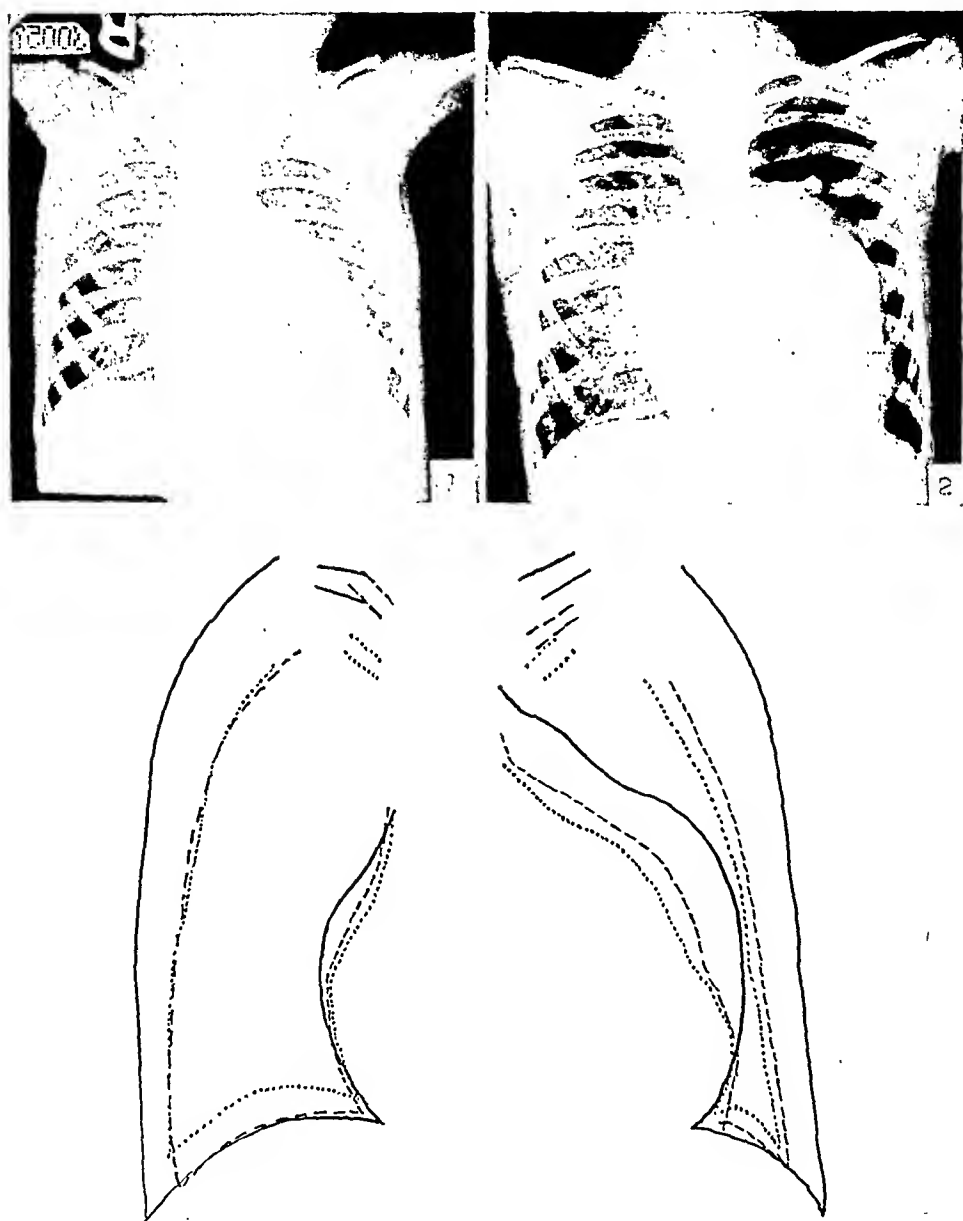


Fig. 6b.—Progressive cardiac enlargement. Case of mitral insufficiency and mitral stenosis. 1, Teleröntgenogram 11/10/30. 2, Teleröntgenogram 3/9/36. 3, Tracings of teleröntgenogram, 11/10/30 . . . . ., 1/5/31 — — — — —, 3/9/36 — — — — —.

broadly speaking, the size of the heart remained constant and the chest grew, with the result that the cardiothoracic ratio decreased.

The fact that the heart was enlarged when the patient first came under observation is a clear indication that there had been previous cardiac strain. In most cases, cardiac enlargement is caused by a combination of dilatation and hypertrophy. Therefore, it is natural that in some cases there was a decrease in the size of the heart before the size became stationary. Furthermore, in a few cases we have seen an

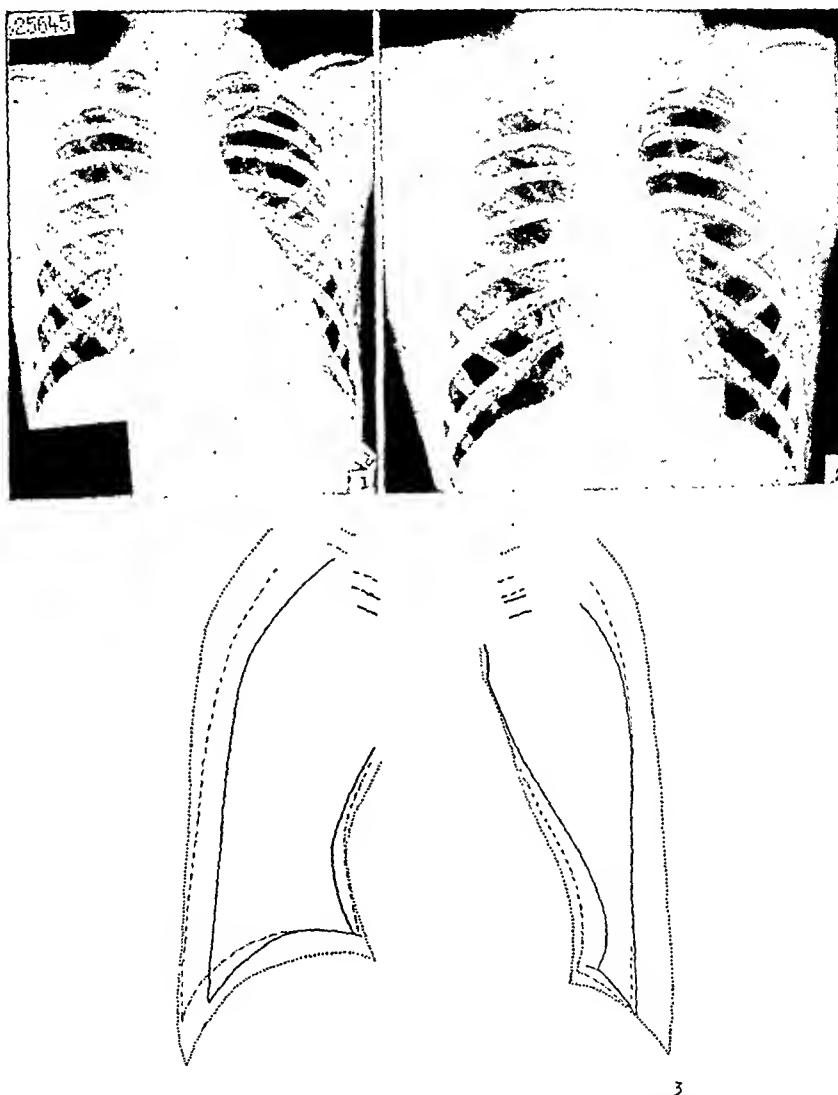


Fig. 7a.—Heart decreased in size. Case 7 (mitral insufficiency and mitral stenosis). 1, Teleroentgenogram 8/13/31. 2, Teleroentgenogram 3/25/35. 3, Tracings of teleroentgenograms 8/13/31 ———, 6/10/32 — . — . — , 3/25/35 . . . . .

additional phenomenon; namely, after the chest had grown sufficiently so that the size of the heart was relatively normal, the heart again increased in size as the chest grew. As is to be expected, this phenomenon was observed in cases in which the heart was not enormously enlarged, and therefore the patient did not have to attain his full growth to enable the size of the heart to return to normal proportions. The following case is an excellent illustration.

TABLE VII

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVI- ATION FROM AV.
August, 1931	13	14.6	22.5	64.8	60	71	9.9	+47.4
October, 1931	13	15.0	22.7	66.1	60	68½	9.9	+51.5
June, 1932	14	12.5	23.5	53.1	60	96	10.2 10.7	+21 +17
May, 1934	16	12.2	26.0	46.9	66½	117	10.6 11.2	+14 + 9
March, 1935	17	12.2	25.8	47.6	67½	121½	11.4	+ 7
March, 1936	18	12.8	27.0	47.4	67½	120½	11.4	+12
June, 1937	19	12.9	27.5	46.9	67½	130	11.7	+10
May, 1938	20	12.6	27.3	46.1	68½	136½	12.0	+ 5
January, 1939	21	13.2	27.0	48.8	68	145½	12.4	+ 7

T.D., Transverse diameter; I.D., internal diameter.

Italicized figures are those given by the insurance company.

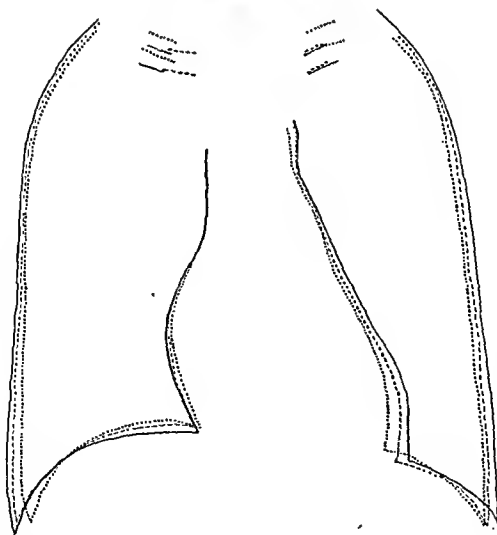
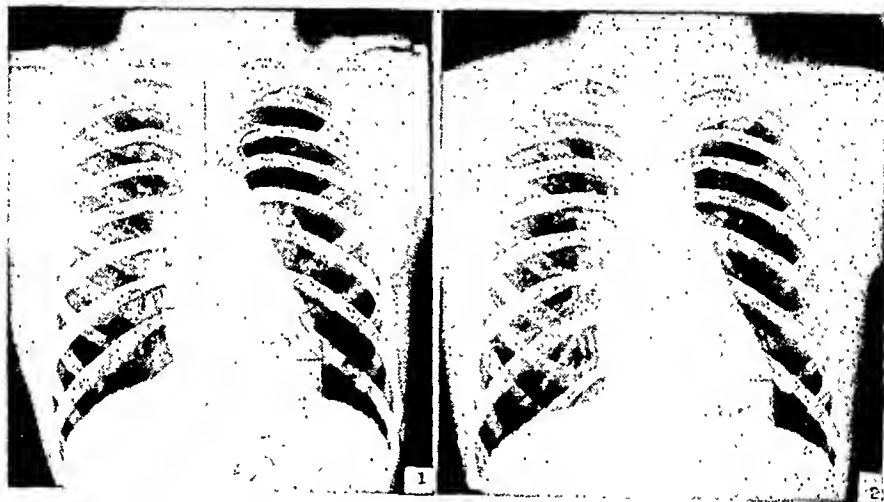


Fig. 7b.—Normal growth. Case 7 (mitral insufficiency and mitral stenosis). 1, Same as Plate 7a, 2. 2, Teleroentgenogram 1/11/39. 3, Tracings of teleroentgenograms 3/25/35 . . . . . (Same as . . . Plate 7a, 3), 6/2/37 — — — — —, 1/11/39



CASE 7.—F. S. (H.L.H. No. 73438), a white boy, was born in 1919. He had scarlet fever at the age of 10 years. His first known rheumatic attack occurred in 1931, when he was brought to the hospital because of dyspnea and abdominal pain. His heart was enlarged; he had a definite mitral insufficiency and a mid-diastolic murmur. His liver extended nearly to the umbilicus. He stayed in the hospital one month, and was then transferred to a convalescent home where he remained five months. Throughout the following year his activity was restricted. By August, 1934, he had developed a definite mitral stenosis. In February, 1935, and again in September, 1938, he had capillary bronchitis. Aside from these two illnesses he has been well and is leading a normal life.

The composite picture of the tracings of the teleroentgenograms is presented in Figs. 7a and 7b. Table VII gives the actual measurements of his heart.

This patient's heart, which was definitely slightly enlarged in August, 1931, and was still the same size in October, 1931, had decreased in size when he returned from the convalescent home in May, 1932. Between 1932 and 1935 the size of the heart remained stationary. Indeed, in 1935 the heart was slightly smaller than it had been in 1932. Between 1935 and 1939 the gradual increase in the size of the heart was consistent with the growth of the body.

In this case the presumptive evidence is that, at the time of the acute attack, part of the enlargement was caused by dilatation. When the dilatation subsided, the "hypertrophy" remained. Finally, when the growth of the body became commensurate with that of the heart, both grew normally.

In all of the cases so far cited, it is obvious that we failed to observe the patient during the period when the heart was enlarging. We have, however, studied this in a number of other cases. In some there has been progressive cardiac enlargement; this group we shall discuss presently. In others the enlargement occurred at irregular intervals.\* In three cases we observed, first, an increase in the size of the heart and then a decrease; and thereafter, over a period of years, the size of the heart remained stationary. One patient had mitral insufficiency and mitral stenosis; another had aortic insufficiency; and a third, at the present time, has no demonstrable valvular lesion. The sequence of events in the third case clearly illustrates the phenomenon. The history is as follows:

CASE 8.—E. H. (H.L.H. No. 65899), a colored boy, was born in 1920. In 1929 he had "grippe," and complained of shortness of breath. In February, 1930, he was first seen at the Harriet Lane Cardiac Clinic, and was found to have rheumatic heart disease, as evidenced by a harsh systolic murmur which was well transmitted to the axilla, and a mid-diastolic murmur. Rest in bed was recommended, but unfortunately he was lost sight of until September, 1930, when he was admitted to the hospital because of cardiac failure. After his discharge from the hospital he was followed in the clinic for two months; then he moved to New York. When he was next seen, in March, 1931, he had polyarthritis, numerous extrasystoles, and congestive heart failure. During the next eight months he had three attacks of heart

\*These cases will be reported later.

failure which required hospitalization for three months, two months, and two months, respectively. During the third admission he received digitalis. It was not until October, 1933, that he was sufficiently improved to be cared for at home. At that time he had a harsh systolic murmur which was well transmitted to the axilla, a short mid-diastolic murmur at the apex, and many extrasystoles; the latter persisted for six months. During 1932 and 1933 his activity was greatly restricted. During the next two years the physical signs of his heart disease became progressively less apparent, and, in 1935, only a soft apical systolic murmur remained. It was not until then that the administration of digitalis could be stopped without causing cardiac dilatation. Since that time he has been well.

The composite picture of the tracings of the teleroentgenograms is presented in Fig. 8a and 8b. Table VIII gives the actual measurements of his heart.

Fig. 8a (3) shows the increase\* in the size of the heart and the decrease in size which followed the administration of digitalis. Fig. 8b, in which the dotted line is a duplicate of that in Fig. 8a, illustrates that after this decrease, the size of the heart remained remarkably constant. From November, 1932, to November, 1938, the transverse diameter of the heart remained virtually stationary, whereas that of the chest increased 5.0 cm. The consequence is that the cardiothoracic ratio decreased from 61.3 to 50 per cent. At the present time there are no murmurs; the heart remains slightly enlarged, but, in comparison with the previous plates, the change is remarkable.

The phenomenon of cardiac dilatation during an acute rheumatic infection is familiar to all. The two cases just cited illustrate how long the dilatation may last. Further, after the dilatation has subsided, the heart may remain enlarged.

Still more important is the fact, which is illustrated by the entire series of cases, that, after the heart has enlarged, the factors which caused the enlargement may disappear and the heart may cease to enlarge. Indeed, it is possible for the size of the heart to remain stationary while the chest grows.

We have observed this phenomenon in twenty-four cases. Five patients, when last seen, had no demonstrable residual valvular damage; six had mitral insufficiency; six, mitral insufficiency and stenosis; one, questionable mitral stenosis; three, aortic insufficiency; and three, aortic insufficiency, mitral insufficiency, and probably mitral stenosis. In 50 per cent, with the growth of the patient the cardiothoracic ratio eventually became 45 per cent or less.

Clinically, the course of the disease in these cases was remarkably satisfactory. By and large, these children did well. Although most of them had more than one attack of acute rheumatic fever before coming under observation, the majority have had no recurrences since that time.

\*Inasmuch as the tremendous increase in the size of the heart raises the question of pericardial effusion, it is worthy of note that none of the doctors on the pediatric or medical service of the Johns Hopkins Hospital who saw the patient thought that there was any evidence of pericardial effusion.

TABLE VIII

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVI- ATION FROM AV.
October, 1930	10	12.9	22.6	57.1	56½	74	9.6	+34
June, 1931	11	17.9	22.7	79.0	58	86½	9.6	+86
November, 1931	11½	14.4	23.2	61.6	58½	86	9.6	+50
April, 1932	12	14.1	23.0	61.3	59	99½	10.0	+41
November, 1932	12	13.5	24.0	56.2	61½	113½	10.5 11.5	+28.5 +17
August, 1933	13	13.9	24.7	57.5	63½	120	10.7 11.7	+30 +19
March, 1934	14	14.6	26.5	55.1	67	140	10.7 12.3	+35 +19
November, 1938	18	14.0	28.0	50.0	70½	164	13.0	+ 7.5

T.D., Transverse diameter; I.D., internal diameter.  
Italicized figures are those given by the insurance company.

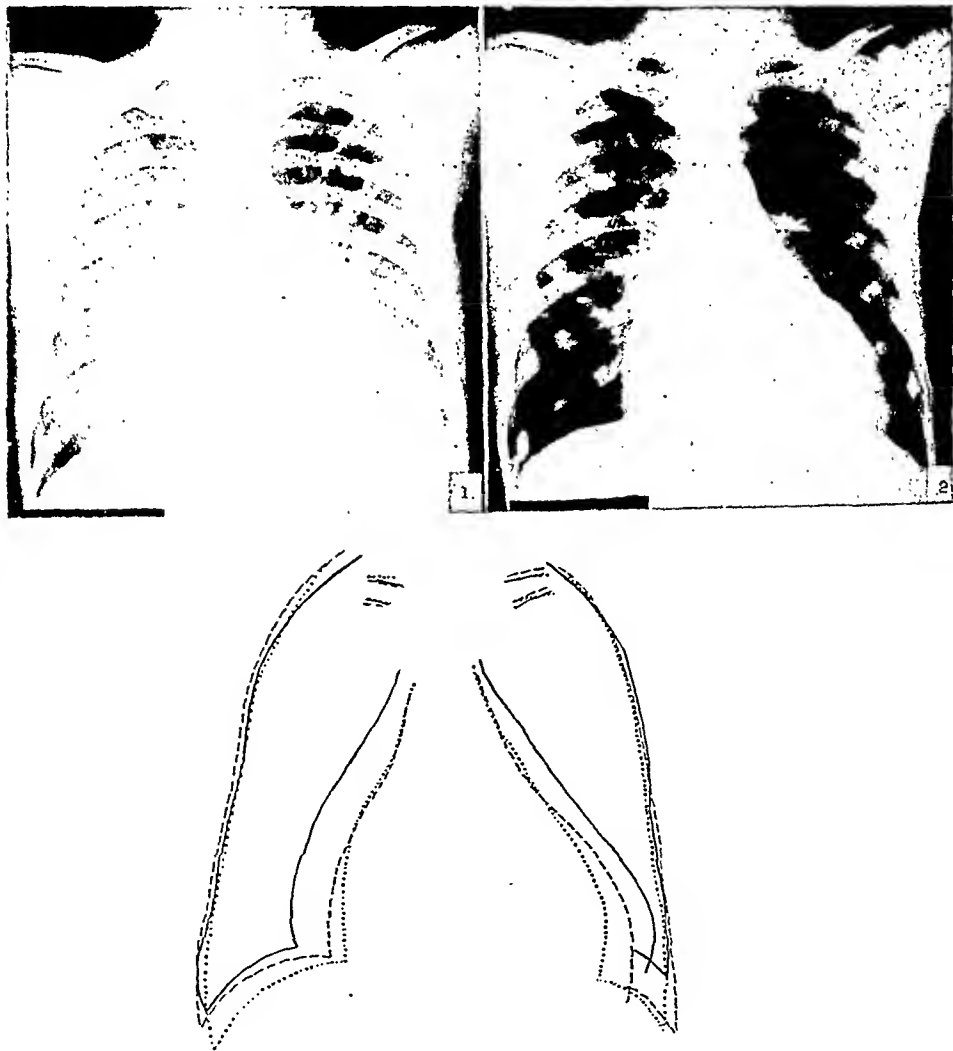


Fig. 8a.—Heart enlarged and decreased in size. Case 8 (severe rheumatic heart disease). 1, teleroentgenogram 6/13/31. 2, Teleroentgenogram 11/6/31. 3, Tracings of teleroentgenograms 10/15/30. . . . . , 6/13/31 — — — — — , 11/6/31 — — — — — .

Six of the children, however, did have recurrences during the period in which the size of the heart remained stationary, and, in addition, in one case (Case 3) the hypertrophy ceased, in spite of the fact that the rheumatic infection remained active for three years. It is worthy of note that all of these children, with the exception of the child who insidiously developed questionable signs of mitral stenosis, were kept at complete bed rest throughout the period of active infection.

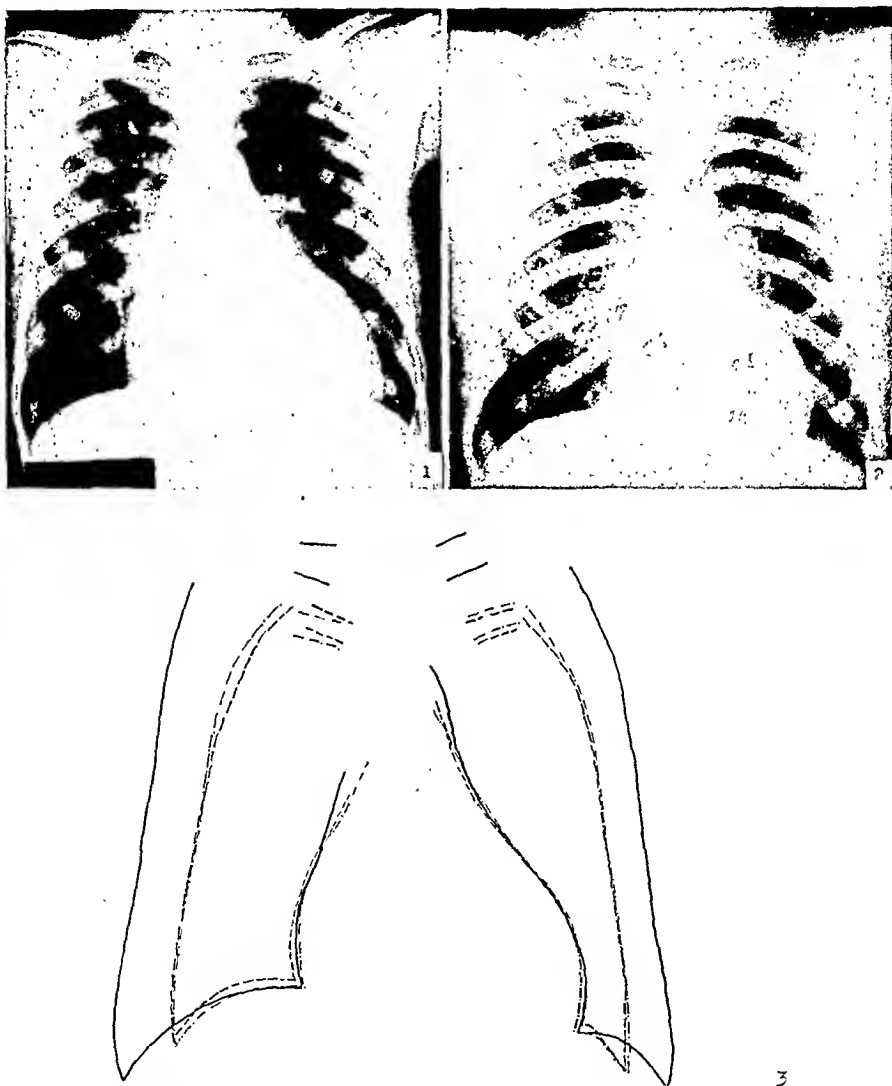


Fig. 8b.—Heart stationary and chest growing. Case 8 (severe rheumatic heart disease). 1, Same as Plate 8a, 2. 2, Teleroentgenogram 4/25/32. 3, Tracings of teleroentgenograms 11/6/31 ———— (Same as ———— Plate 8a, 3); 4/25/32 — . . . ; 11/2/38 ————.

In this entire group there were but three deaths—two from subacute bacterial endocarditis and one from acute rheumatic fever. The latter occurred in the case of a boy who had had a severe infection which had resulted in tremendous cardiac enlargement, pronounced aortic in-

sufficiency, and clinical signs of adhesive mediastinitis. For three years the size of the heart remained stationary while the chest grew, and the cardiothoracic ratio decreased from 64 to 60 per cent. The following year he developed rheumatic pancarditis and died.

The mortality rate in this group was low, namely, 12.5 per cent. Two children (approximately 10 per cent) still show signs of active rheumatic infection, and are at rest in bed. The remaining children (77.5 per cent) show no signs of rheumatic activity, and are leading normal, active lives.

#### PROGRESSIVE CARDIAC ENLARGEMENT

The third group showed an entirely different phenomenon. In these cases, the heart, which was already enlarged when the patient first came under observation, continued to enlarge progressively. We have observed this sequence of events in sixteen cases. From this group we excluded not only all cases of pericardial effusion, but also all cases in which there was any evidence of adhesive mediastinitis. Exclusion of the latter was deemed advisable because of the possibility that adhesion between the heart and the chest might cause cardiac enlargement. The phenomenon of progressive cardiac enlargement is familiar. Two cases will suffice as illustrations.

CASE 9.—A. C. (H.L.H. No. 56627), a colored girl, was born in 1928. In January, 1933, she first complained of joint pains. She was not seen, however, until June, 1933, at which time she had severe heart failure. Her heart was enormously enlarged, and she had a systolic murmur and a mid-diastolic murmur. She was in the Provident Hospital for three months. Her first stay at the Harriet Lane Home lasted from September, 1933, to March, 1934. Throughout the next four years she had repeated exacerbations of rheumatic fever which necessitated readmission to the hospital. In March, 1938, she died. Autopsy showed chronic rheumatic heart disease, with Aschoff bodies throughout the myocardium.

The composite picture of the tracings of the teleroentgenograms is presented in Fig. 9. The actual measurements of the size of the heart and the size of the chest are given in Table IX.

It is clear that, in this case, the heart increased in size more rapidly than the chest. Case 10 illustrates the same phenomenon.

CASE 10.—D. H. (H.L.H. No. 52720), a colored girl, was born in 1925. She was first examined in 1932, because of tuberculosis. A teleroentgenogram which was taken at that time showed a small heart; the cardiothoracic ratio was 42.0 per cent. In the spring of 1937 she apparently had her first attack of acute rheumatic fever. At that time the size of her heart was found to be within the upper limits of normal, and the murmur was regarded as functional. She was lost sight of for a year. In June, 1938, she returned with the complaint that one of her knees had been swollen for two months. Her heart was found to be enlarged, and she had a harsh, blowing systolic murmur and a mid-diastolic murmur. Rest in bed was advised, but it was impossible to obtain the cooperation of the patient.

TABLE IX

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVI- ATION FROM AV.
December, 1933	5	12.8	19.5	65.6		44½	8.5	+50
June, 1934	6	12.3	19.5	63.0	45	51	8.6	+46.5
October, 1935	7	14.7	21.6	68.6	50½	64	9.2	+60
March, 1936	8	14.6	22.2	65.7	50½	71½	9.2	+60
November, 1937	9	16.0	22.0	71.1	52½	65½	9.3	+72
February, 1938	10	15.2	22.5	67.5	53	67	9.5	+60

T.D., Transverse diameter; I.D., internal diameter.

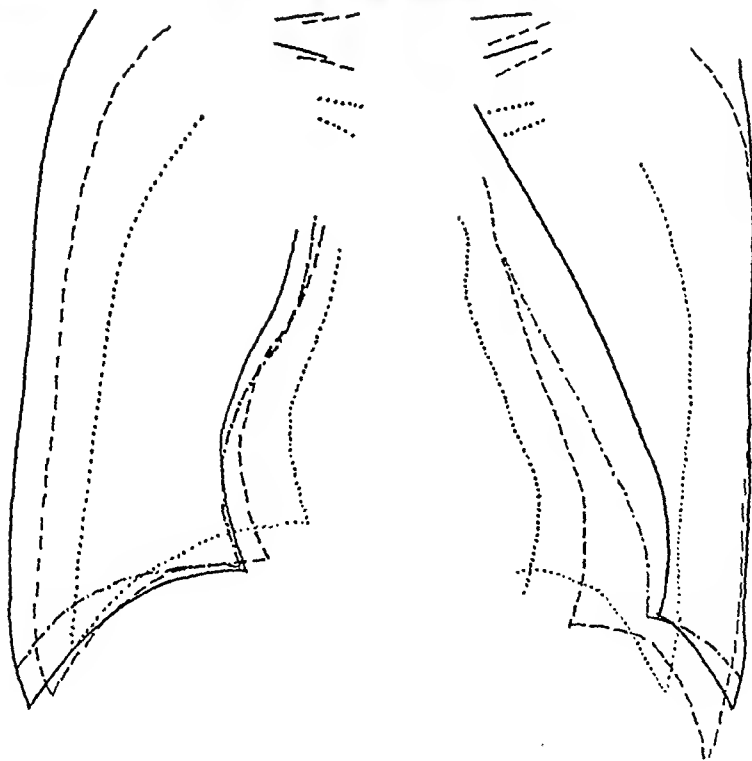
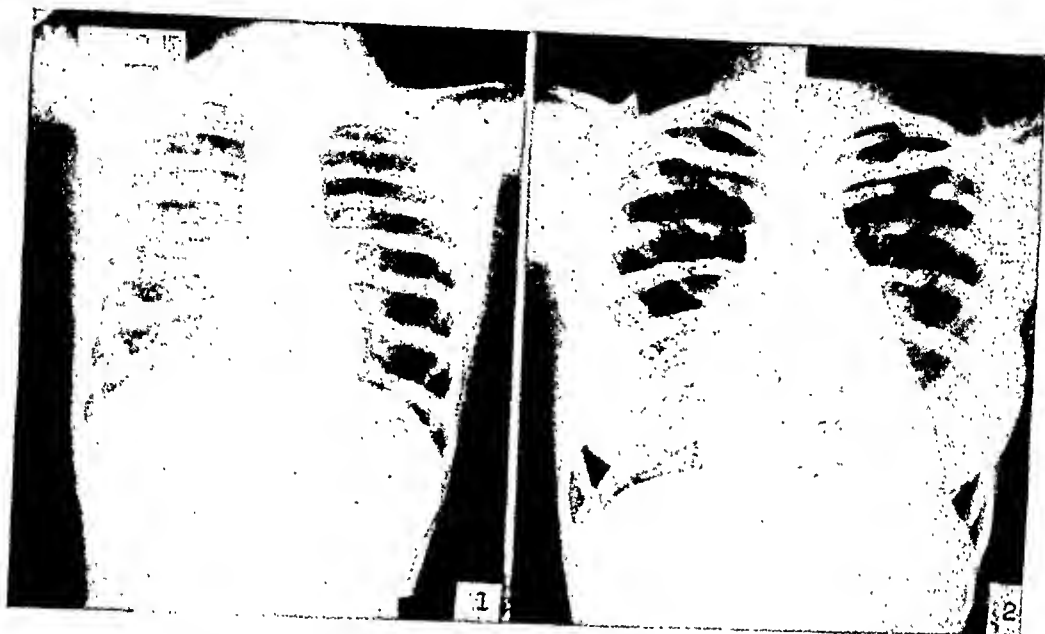


Fig. 9.—Progressive cardiac enlargement. Case 9 (rheumatic myocarditis, with slight mitral insufficiency). 1, Teleroentgenogram 6/21/34. 2, Teleroentgenogram 2/4/38. 3, Tracings of teleroentgenograms 6/21/34 . . . . ., 3/13/36 — — — — —, 2/4/38

TABLE X

DATE	AGE (YR.)	HEART T.D. (CM.)	CHEST I.D. (CM.)	C/T	HEIGHT (IN.)	WEIGHT (LB.)	AV. T.D. OF HEART (CM.)	PER CENT DEVI- ATION FROM AV.
May, 1932	7	7.3	17.0	42.0				
July, 1937	12	9.9	20.2	48.5			9.0	-19
November, 1938	13	12.2	21.1	57.6	57	52½	9.8	+14
February, 1939	14	13.0	22.0	59.1	58	72½	9.8	+24.4
						78	10.0	+30

T.D., Transverse diameter; I.D., internal diameter.



3

Fig. 10.—Progressive cardiac enlargement. Case 10 (mitral insufficiency and questionable mitral stenosis). 1, Teleroentgenogram 5/17/32. 2, Teleroentgenogram 2/17/39. 3, Tracings of teleroentgenograms 5/17/32 . . . . ., 7/28/37 — — — — —, 11/30/38 — — — — —, 2/17/39 — — — — —.

The composite picture of the tracings of the teleroentgenograms is presented in Fig. 10. The actual measurements of the size of the heart and the size of the chest are given in Table X.

This case not only illustrates the rapidity with which the heart may enlarge, but, also, a comparison with the first teleroentgenogram, which was taken before the onset of rheumatic fever, illustrates how great the cardiac enlargement may become before it exceeds the theoretical upper limit of normal.

Obviously, these teleroentgenograms show a sequence of events which is quite different from that in either of the two preceding groups. The time required for the enlargement to develop varied from six months to five years. In cases of gradual progressive enlargement, it is clear that the heart enlarged out of proportion to the growth of the chest.

The type and severity of the valvular lesions in this group do not differ greatly from those in the preceding group. Two patients had mitral insufficiency; three, mitral and aortic insufficiency; two, mitral insufficiency and slight mitral stenosis; five, mitral insufficiency and definite mitral stenosis; and one, mitral and aortic insufficiency and stenosis. In two cases the rheumatic infection was believed to be superimposed upon a congenital malformation of the heart, namely, an interauricular septal defect. Another child may also have congenital malformation, for the murmur was first heard when he was 15 months of age; at the present time, however, his physical signs are characteristic of mitral insufficiency and mitral stenosis.

Clinically, the course of the disease in this group was profoundly different from that in either of the two preceding groups. Eight of the sixteen patients died, all of active rheumatic infection. In six of the cases the diagnosis was confirmed by autopsy. Although, in the other two, no autopsy was done, both children died of pancarditis. Of the remaining children, four are chronic invalids, and two have no complaints but still show evidence of an active rheumatic infection. The two remaining children have had repeated exacerbations of rheumatic fever, with only brief periods when they were free from infection.

Thus, among the children who showed progressive cardiac enlargement, the mortality rate was 50 per cent; in addition, 25 per cent are chronic invalids. The remaining 25 per cent, although they are not critically ill, have had repeated attacks of rheumatic fever, or have shown laboratory evidence of a persistently active infection.

#### DISCUSSION

These studies illustrate that there are at least three different and distinct sequences of events relative to the size of the heart in acute rheumatic fever. First, a heart which has never been enlarged may



show normal growth. Second, after a period of initial enlargement, it is possible for the heart to remain stationary in size while the chest grows. Third, there may be progressive cardiac enlargement.

The fact that the changes in the size of the heart may show different sequences in cases in which the valvular lesions are similar indicates that the valvular lesions are not the prime cause of cardiac enlargement. Indeed, in the first group, there were a number of subjects with persistent valvular damage whose hearts had never been enlarged; the increase in the size of their hearts was commensurate with normal growth. For example, in Case 2 the signs of aortic insufficiency persisted for seven years without demonstrable alteration in the size of the heart. In the second group, i.e., those patients in whom hypertrophy ceased, the majority of the patients showed definite signs of chronic valvular damage. These observations are in accord with the opinion expressed by Lewis,<sup>5</sup> namely, that the valvular lesion is of far less importance than the condition of the myocardium.

Lewis<sup>5</sup> and Palmer<sup>2</sup> have shown that, in adults, the heart enlarges as the result of an increase in the cardiac load and that, once the heart has adjusted itself to the new conditions, no further enlargement occurs. A notable example of this phenomenon is coarctation of the aorta; in spite of the persistent, sometimes extreme, hypertension, the heart does not undergo progressive enlargement. Our studies indicate that, fundamentally, the same is true in children with rheumatic fever, i.e., that cardiac enlargement occurs during periods of active rheumatic infection, and that, when the infection has subsided and the heart has adjusted itself to the valvular lesions, there is no further increase in the size of the heart other than that which is commensurate with normal growth.

The next question which presents itself is concerned with the relation of acute myocarditis to the increase in the size of the heart. All of our patients who showed cardiac enlargement had had an active rheumatic infection. Further, all those who showed progressive cardiac enlargement had signs of a persistent, active infection. The reverse is not true. Not all patients with an active infection have shown progressive cardiac enlargement. On the contrary, some never had demonstrable cardiac enlargement, and, in other cases, the enlargement ceased to exist.

The fact that cardiac enlargement can cease to exist although the active infection persists indicates that cardiac enlargement depends not only on the severity and duration of the disease, but also, in many instances, upon the work demanded of the diseased heart. For example, in Case 3, although the signs of active infection persisted for three years, the heart ceased to enlarge when the patient was put to bed.

It seems to us highly significant that, in every instance, with the exception of the child in the first group who insidiously developed signs of

mitral stenosis, all of the patients who had active rheumatic infection without demonstrable increase in the size of the heart were kept at complete bed rest throughout the active infection. This observation is the more significant because these cases were grouped solely on the basis of changes in the teleroentgenogram. After so doing, it was found that the children in whom cardiac enlargement came to an end were those who had had long periods of rest in bed. Although one cannot prove that rest was the decisive factor, the above observation strongly suggests that the degree of cardiac enlargement can be altered by treatment with rest in bed.

Inasmuch as, in a number of cases, signs of active rheumatic infection persisted for months after the heart ceased to enlarge, we believe that cardiac enlargement depends, to a large extent, on the load placed upon the heart during the period in which it is weakened by the acute or subacute myocarditis. It appears that the diseased heart is frequently unable to carry the load caused by ordinary physical exertion, and therefore undergoes hypertrophy. In such cases, if the patient is put to bed and the work required of the heart is thus lessened, the heart ceases to hypertrophy.

How great the enlargement may be is illustrated by the fact that, after the infection has subsided, the heart may be sufficiently large to meet the needs of the body for a number of years (for example, in Case 8, for six years). Under these circumstances there is no further increase in the size of the heart even when the patient is still growing, and is leading a normal, active life. It seems that, when the factors which caused cardiac enlargement cease to operate, the stimulus to the growth of that organ is withdrawn until such time as the growth of the body has become commensurate with that which occurred in the heart during the period of unusually great strain; thereafter there is a resumption of the normal rate of growth. Case 7 illustrates this phenomenon. This observation suggests that there is no essential difference between "hypertrophy" of the heart in response to an abnormal stimulus and normal "growth." It appears to be fundamentally a question of *rate* of growth.

Another illustration of this phenomenon was found in two cases in which the patients were followed over a period of years, and ultimately died. Both children, when they were first seen, had severe rheumatic infections, and their hearts were 30 per cent above the normal size for their age and height. Case 3 records the history of one of these children. In each instance, over a period of years, the heart remained stationary in size and the child grew, with the result that the size of the heart again came to lie within normal limits. Subsequently, each developed a *Streptococcus viridans* infection. At autopsy the hearts were found to be of approximately normal size; had either of the children died at an earlier date, the heart would have been described as "large for a child."

These observations afford confirmatory evidence of the validity of the observations based on teleroentgenograms.

The sequence of events is not always as clear as in the cases here reported. We have observed a large number of cases in which there was a slight increase or slight decrease in the size of the heart. In such cases it is difficult, if not impossible, to ascertain whether the decrease in size was a chance variation or whether the slight increase was caused by dilatation. In other cases, after the heart had enlarged, it remained stationary in size and then enlarged again. These cases will be reported later.

The observations reported in the present paper, although of a different nature, are in accord with those of Bland, Jones, and White<sup>6</sup> concerning disappearance of the physical signs of rheumatic heart disease. Their observations were based on physical examination and did not include teleroentgenograms. Case 8 illustrates the phenomenon reported by them. This boy had, for many years, both a harsh systolic murmur and a long mid-diastolic murmur; eventually both murmurs disappeared. The case is in no sense unique. It is, however, a dramatic example of the amount of improvement which is possible, even after repeated attacks of acute rheumatic fever. Our studies bring to light an additional factor; not only may murmurs disappear, but "hypertrophy" may also disappear.

Our third group of cases, in which there was progressive cardiac enlargement, illustrates a more familiar sequence of events—so familiar, in fact, that it is often considered inevitable. The children in this group suffered from severe infection of long duration. The severity of the infection is undoubtedly of great importance. Nevertheless, inasmuch as many patients in the second group also suffered from protracted, severe infections, it seems probable that one important reason for the unfavorable outcome in the third group was unrestricted activity. Some children undoubtedly have such a severe infection that rest in bed will not alter the course of the disease. Nevertheless, it seems to us highly significant that only 50 per cent of the children in the third group were kept in bed, and these for only short periods during the acute stage of their illness. The remainder had no rest in bed until their terminal illness.

The high mortality rate and the high incidence of chronic invalidism in the third group indicate all too clearly the serious prognosis in those cases in which there is progressive cardiac enlargement. In this group the mortality rate was 50 per cent, and an additional 25 per cent are chronic invalids. These figures present a striking contrast to the course of the disease in the two preceding groups, in which the mortality rate was approximately 10 per cent; an additional 10 per cent still have active infections, but 80 per cent of the children are well and are leading active lives.

These differences in the mortality rate speak for themselves. There is no question as to the goal for which one should strive. If successive teleroentgenograms indicate that the size of the heart has increased out of proportion to the growth of the child, it is clear evidence of an unfavorable sequence of events. It is, in itself, presumptive evidence that the child suffers from an active infection. Certainly, under such circumstances the work demanded of the heart should be kept at a minimum by rest in bed. Once the infection has been overcome, the heart readily adjusts itself to the increased load caused by the valvular damage, and thereafter there should be no further cardiac enlargement. For such patients the outlook is excellent; they may hope to lead normal, active lives.

#### CONCLUSIONS

1. By superimposing teleroentgenograms, one may obtain valuable information concerning the course of a rheumatic infection.

2. This method of study has revealed three distinct kinds of changes in the size of the heart: (1) It may grow normally; (2) it may, after a period of enlargement, remain stationary in size while the chest grows; and (3) it may enlarge progressively.

3. These observations prove that, in the course of the rheumatic infections, cardiac enlargement is not an inevitable, gradual, progressive process; even in the presence of valvular damage, enlargement can occur and then cease.

4. The fact that all types of valvular lesions were found in our second and third groups indicates that the size of the heart does not depend primarily on the nature of the valvular lesion.

5. Evidence is brought forward that cardiac enlargement is directly related to activity of the rheumatic infection.

6. The fact that, in some cases, in spite of severe infection, the heart did not enlarge proves that active rheumatic infection does not inevitably cause cardiac enlargement.

7. Inasmuch as, in the majority of cases in which there was no cardiac enlargement during known periods of active infection, the patients were kept at complete bed rest, the load placed on the heart during the active infection must be an important factor.

8. The mortality rate among the patients who showed progressive cardiac enlargement was much higher than in the other two groups. In the first two groups the mortality rate was 7 to 13 per cent; 80 per cent of the patients are well. In the third group the mortality rate was 50 per cent; in addition, 25 per cent of these patients are chronic invalids; in only 25 per cent of the cases is the condition of the patient in any sense satisfactory.

9. The occurrence of progressive cardiac enlargement in the course of rheumatic fever is a serious phenomenon. It is strong presumptive

evidence of the existence of a persistent active infection and is a clear indication that the load on the heart should be reduced to a minimum by keeping the patient at complete bed rest.

10. Once the rheumatic activity has subsided and the heart has adjusted itself to the valvular lesions, there should be no further cardiac enlargement other than that which is commensurate with normal growth.

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#### DISCUSSION

DR. M. A. KUGEL, Miami Beach, Florida.—I want to thank Dr. Taussig very much for her report on enlargement of the heart. I think this problem becomes simpler when we appreciate the physiologic mechanism involved. All agree that an enlarged heart usually gives more concern than a heart that is not enlarged. We can go back to the work of Müller, and many others, who studied the inflow and outflow tracts, for enlightenment as to the causes of cardiac enlargement. The heart does not enlarge beyond normal limits unless there is some underlying pathologic-physiologic disturbance. If the myocardium is normal, under certain conditions only hypertrophy develops. However, if, in addition to increased work, there is either ischemia caused by coronary thrombosis or anemia, or extensive myocardial disease as a result of infection, the heart will enlarge greatly.

Nature performs that experiment very well for us. One should remember that, in mitral stenosis, even when an acute rheumatic infection is present, the left ventricle, despite the fact that it is affected, will usually be small, whereas the left auricle and right ventricle, and even the right auricle, will be large. Therefore, we have an experiment in nature, in which, with a diseased heart, that part of the heart which has less work to do will not enlarge as much as the part that has more work to do.

In a group of cases of so-called idiopathic hypertrophy of the heart, which I described a number of years ago, evidence of myocardial disease was found invariably. We can assume clinically, and from our pathologic experience, that enlargement of the heart, even in a case of hypertension, means more than just increased work. It indicates either lack of circulation, or myocardial disease caused by infection or coronary disease.

DR. HELEN B. TAUSSIG, Baltimore.—We agree with Dr. Kugel that an increased load upon the heart causes enlargement. This is in accord with Sir Thomas Lewis's studies, which show that it is not the constant load, but an increased amount of work and increased strain, which causes cardiac enlargement. The heart

readily adjusts itself to the residual valvular lesions. I don't mean to say that there is no enlargement, but the enlargement caused by valvular damage is surprisingly slight.

Our studies are also in accord with Dr. Duckett Jones's observations concerning the regression of physical signs and the amount of improvement which may occur in cases of rheumatic fever and rheumatic heart disease.

In conclusion, let me repeat that we feel that severe, active infection is the cause of damage, and, further, that increasing the strain upon the heart when an active infection is present is making matters very much worse. For that reason we urge absolute rest in bed throughout the period of active infection.

# METASTATIC BRONCHIOGENIC CARCINOMA OF THE HEART

## REPORT OF CASE, WITH CLINICAL DIAGNOSIS BY PROGRESSIVE ELECTRO-CARDIOGRAPHIC CHANGES, AND PATHOLOGIC CONFIRMATION

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**M**OST of the tumors of the heart and pericardium are asymptomatic and are, therefore, of interest only to the pathologist. Some, however, are the cause of cardiac dysfunction and present clinical features pointing to such involvement. A review of the clinical histories of these cases shows that neoplasm might be suspected if the clinician bears this possibility in mind.

In a comprehensive review of the literature, Yater,<sup>1</sup> in 1931, published numerous autopsy series that have been investigated in regard to the occurrence of cardiac metastases, and he concluded that tumors of the heart and pericardium are rare. More recently, several additional series have been published, from which it would appear that they are more common than believed. Pollia and Gogol<sup>2</sup> found twenty-nine secondary tumors of the heart among 12,000 autopsies, 1,450 of which were malignant tumors, an incidence of 2 per cent invasion in cases of malignancy. In a study of 327 autopsies on patients with known malignancy, Burke<sup>3</sup> found fourteen cases of metastatic involvement of the heart, constituting approximately 4.3 per cent of routine autopsies made in such cases at the State Institute for the Study of Malignant Disease, New York. Finally, the highest incidence yet published was found by Scott and Garvin<sup>4</sup> at the Cleveland City Hospital. Among 1,082 cases of malignant disease appearing in their series of 11,000 consecutive post-mortem examinations, these authors found the heart, the parietal pericardium, or both, involved in 118 cases, an incidence of 10.9 per cent invasion in cases of malignancy.

Metastases to the heart have occurred from neoplasms of all the main organs. Scott and Garvin<sup>4</sup> found that carcinoma of the bronchus and of the breast is of paramount importance as a source of secondary tumors of the heart and pericardium, the incidence of involvement being 35.6 per cent in both instances. The mechanism of implantation of tumor tissue in the heart must vary considerably in individual cases. Most of them are associated with primary or secondary intrathoracic tumors, from which the tumor cells may gain access to the left side of the heart through the pulmonary veins and thence to the coronary arteries and the cardiac muscles. In the less common cases of implantation on

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the endocardium of the right side of the heart, the tumor cells probably gain entrance to the blood stream from the lymphatic duct and pass to the superior vena cava via the bronchial or azygos veins. Where the lymph nodes in close proximity to the heart itself are involved, as in the case of the tracheobronchial lymph nodes which drain the pericardium as well as the pleura, retrograde conduction along the lymphatic channels would allow a direct growth of the tumor cells backward to the heart muscle. In all cases of direct extension, the lymphatics may or may not play an important role.

The clinical features of neoplastic involvement of the heart have been well classified by Yater.<sup>1</sup> He groups these cases logically into those in which the clinical type is not suggestive of tumors of the heart and those in which the type is suggestive of such a diagnosis. Under the first type are those in which there is sudden death, terminal cardiac embarrassment, symptoms of congestive heart failure, or symptoms suggestive of subacute bacterial endocarditis. In the second group there are various abnormalities of rhythm, symptoms of congestive heart failure which develop without apparent cause in a patient with a known malignant process, accumulation of hemorrhagic fluid in the pericardial sac,<sup>1, 5-7</sup> and lastly, suggestive roentgenologic signs.<sup>5</sup> Frequently, a murmur which is believed to be typical of mitral stenosis is found.<sup>8-10</sup> This is often due to a pedunculated tumor of the right or left auricle, causing a functional stenosis of the tricuspid or mitral orifice with certain changes in position. It is also in these cases that sudden death occurs.

In patients with known malignancy, the sudden appearance of paroxysmal auricular tachycardia or paroxysmal auricular fibrillation or flutter<sup>4, 11</sup> is suggestive of cardiac tumor with involvement of the atria. The most common type of cardiac abnormality, however, has been associated involvement of some portion of the conduction system. These patients have shown bundle branch block,<sup>1, 7, 12</sup> frequently, various degrees of A-V block,<sup>13</sup> and even complete A-V dissociation<sup>1, 5</sup> with the Stokes-Adams syndrome, have been found.

Barnes and associates<sup>5</sup> conclude that "on the basis of published tracings and on theoretical grounds, it is to be anticipated that most of the electrocardiographic changes that will be observed in cases of tumor of the heart will result from neoplastic invasion of the ventricles. It is probable that invasion of the conducting system will account for a majority of the abnormal electrocardiograms. Because of the more frequent invasion by tumors of the right ventricle than of the left,<sup>11, 12, 14</sup> right bundle branch defects should exceed those of the left bundle branch. Invasion of the muscle of the left ventricle without involvement of the bundle branches or of the pericardium should produce tracings closely similar to those obtained in the fibrotic stage following acute myocardial infarction (case of Siegel and Young<sup>15</sup>). Invasion of



the epicardium,<sup>6</sup> either alone or in conjunction with involvement of the ventricles, may produce or modify changes in the waves. If a patient, known to have had a neoplasm, more or less suddenly exhibits these electrocardiographic changes in the absence of any other pathological processes in the heart to explain them, then they contribute important presumptive evidence that the malignant process has invaded the heart."

A search of the literature reveals only eight cases of secondary tumors of the heart diagnosed during life,<sup>4, 8, 11, 12</sup> and to this group is added the case herein presented.

#### CASE REPORT

B. McC., a 63-year-old white male, was admitted to the Medical Service of the Queens General Hospital on Aug. 7, 1939, complaining of pain in the left anterior chest.

The past history included pneumonia many years previously and an admission to the genitourinary service of this hospital on March 20, 1939, for suprapubic prostatectomy. During the latter admission, roentgenologic examination of the chest on March 27, 1939 (Fig. 1), revealed no marked or unusual findings except increased hilar markings, and an electrocardiogram on March 21, 1939 (Fig. 6), showed regular sinus rhythm and vertical axis deviation.

The patient was discharged from the hospital on May 18, 1939. On June 22, 1939, he came to the outpatient department complaining of nonproductive cough, associated with pain in the left upper chest and back, and increasing dyspnea and wheezing (asthmatoïd breathing), which had appeared one week following his discharge from the hospital. Examination revealed some dullness and diminished breath sounds in the left upper chest posteriorly. A roentgenologic examination on the same day (Fig. 2) disclosed no change from the findings of the previous examination.

At the time of his admission on Aug. 7, 1939, the patient gave a history that one week prior he had developed severe pain in the left chest anteriorly, constricting in nature and radiating to the left axilla. He stated that the pain was relieved after one hour by the application of a mustard plaster. He applied at the outpatient department, where examination showed a marked irregularity of the heart (auricular fibrillation), and he was admitted to the medical ward with a diagnosis of possible coronary occlusion. Examination several hours later revealed wheezing respirations, more marked on the left side; the heart was not enlarged; there was regular sinus rhythm, and the blood pressure was 100/60.

A roentgenologic examination of the chest on Aug. 14, 1939 (Fig. 3), disclosed considerable increase in the left hilar markings as compared with the previous films. The heart and aorta were normal as to size, shape, and position.

An electrocardiogram on Aug. 10, 1939 (Fig. 7), revealed regular sinus rhythm, with the QRS low and notched, and diphasic T and Q waves present in Lead III. On Aug. 14, 1939, fibrillation was noted again, and the impression arose that the initial onset of pain one week before admission might be explained on the basis of a paroxysmal auricular fibrillation. Digitalis and quinidine therapy was instituted, with marked subjective improvement, and the patient was allowed up and around the ward.

Another roentgenologic examination of the chest on Aug. 21, 1939 (Fig. 4), showed the peribronchial thickening of the left hilar region to be more marked than at any time since March 27, 1939, and the possibility of fibrotic tuberculous infiltration of the upper lobe of the left lung was suggested. The heart and aorta were normal.

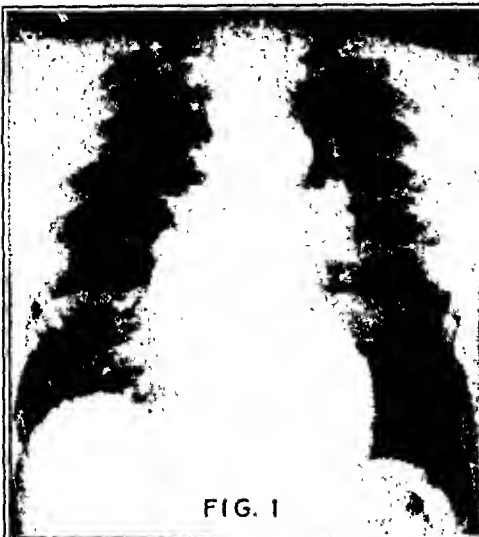


FIG. 1

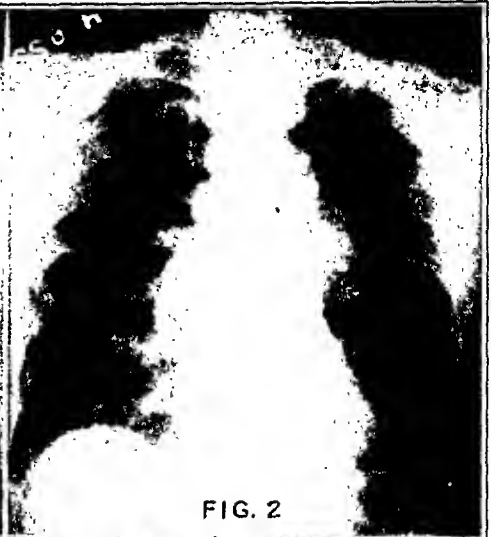


FIG. 2

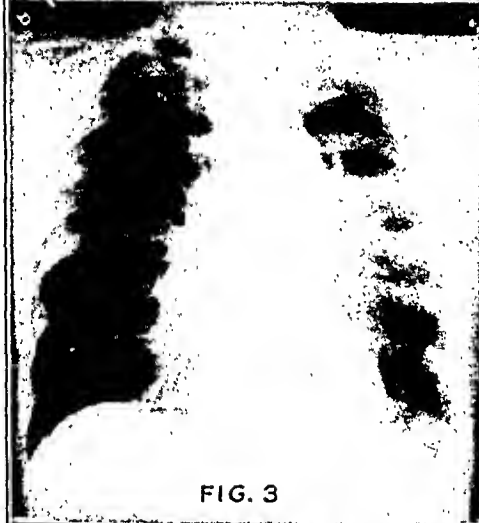


FIG. 3

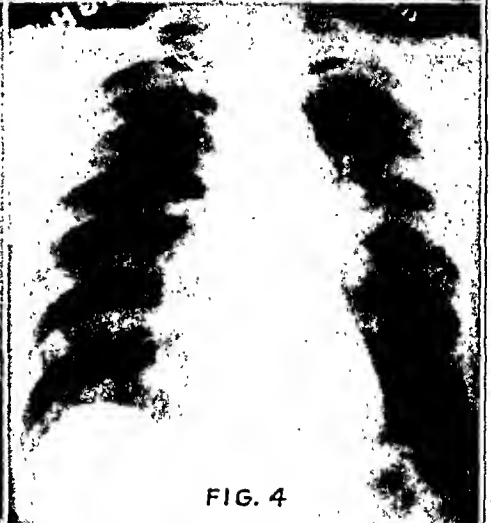


FIG. 4

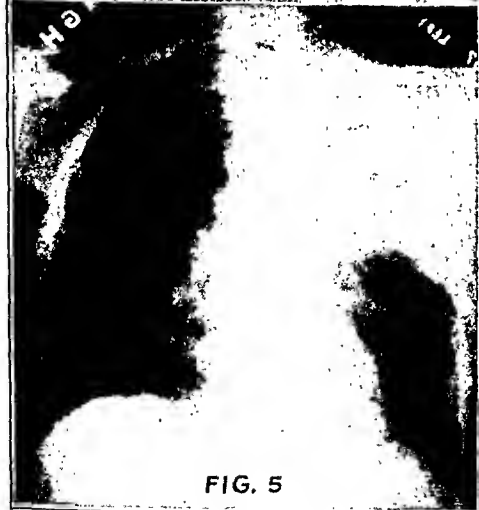


FIG. 5

Fig. 1.—Roentgenogram taken March 27, 1939, when the patient was on the genitourinary service.

Fig. 2.—Roentgenogram taken in the outpatient department on June 22, 1939.

Fig. 3.—Roentgenogram taken Aug. 14, 1939.

Fig. 4.—Roentgenogram taken Aug. 21, 1939.

Fig. 5.—Roentgenogram taken Sept. 21, 1939.

On Aug. 29, 1939, the patient again developed cough and pain in the left anterior chest, and for the first time there was a temperature of  $100.6^{\circ}$  F. On the following day the temperature rose to  $102.4^{\circ}$  F., and examination again revealed dullness and diminished breath sounds over the upper lobe of the left lung posteriorly. From this time to the day of death there were daily fluctuations of temperature up to  $103^{\circ}$  F. On Sept. 1, 1939, the cough was accompanied by bloodstreaked sputum, and for the first time, a high-pitched, "sea-gull," systolic murmur was heard at the apex of the heart, associated with a thrill. On this day another electrocardiogram, which had been taken on Aug. 28, 1939 (Fig. 8), was reported and showed incomplete

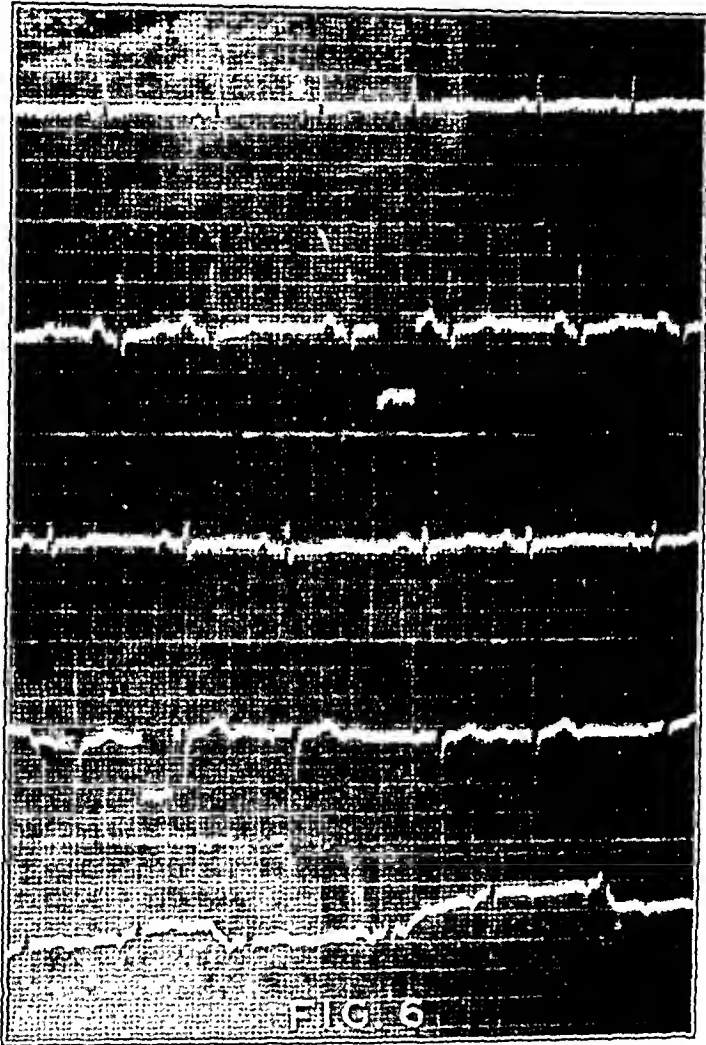


Fig. 6.—Electrocardiogram taken March 21, 1939, when the patient was on the genitourinary service.

left bundle branch block, with the QRS complexes slurred and widened (0.14 sec.) and with S-T depression and upright T waves in all standard leads. At this time, in view of the electrocardiographic changes, it was thought that there might have been a coronary occlusion at the onset, with involvement and possible perforation of the interventricular septum (thus accounting for the peculiar murmur), with the lung signs secondary to pulmonary infarction. However, the cough, the blood-streaked sputum, the fever, and the physical findings persisted far beyond the usual expected period for such conditions; consequently, another roentgenologic examination of the chest was done on Sept. 21, 1939 (Fig. 5), and this revealed marked in-

creased density in the upper third of the left lung field, with atelectasis, displacement of the mediastinum to the left, and contraction of the left upper thorax. A cavity was also noted at the level of the second intercostal space, in the midclavicular line.

A review of the clinical course, in view of these findings, revealed that from the onset this case must have been one of bronchiogenic carcinoma of the left upper lobe bronchus, and that the cardiac signs could now be best explained as metastatic involvement of the conduction system of the left ventricle. Soon, recurrent attacks of complete heart block occurred and, together with the peculiar murmur heard, presented presumptive evidence of neoplastic involvement of the interventricular septum. Finally, the complete heart block became persistent (electrocardiogram on Oct. 16, 1939 (Fig. 9). On the day prior to death there occurred two typical attacks of Stokes-Adams syndrome. The patient died suddenly on Oct. 23, 1939.

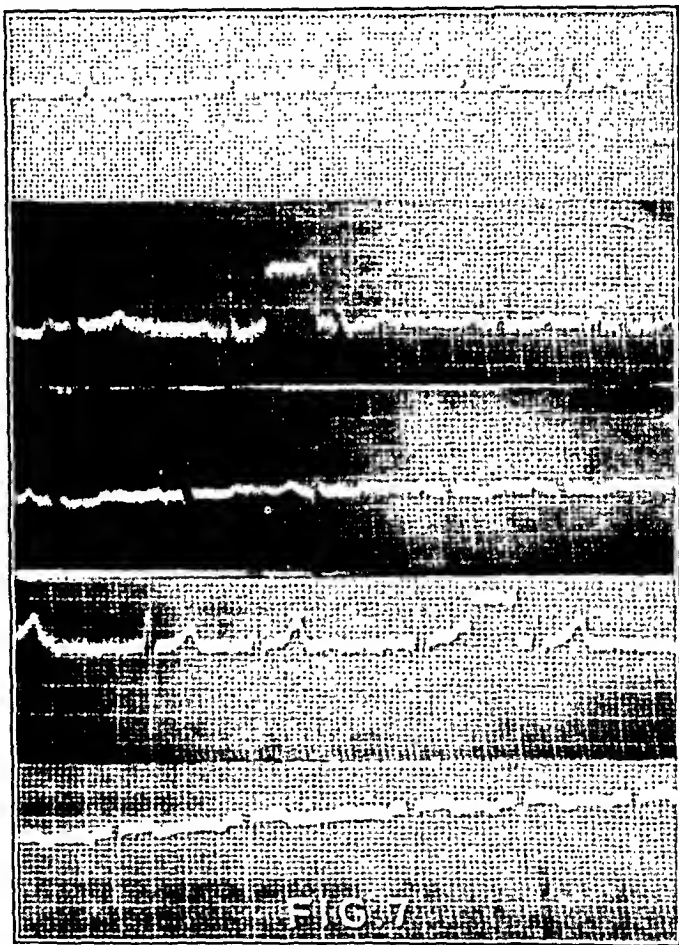


Fig. 7.—Electrocardiogram taken Aug. 10, 1939.

The clinical diagnosis was: (1) bronchiogenic carcinoma of the left upper lobe bronchus, with abscess cavitation; (2) metastasis to the heart, particularly involving the interventricular septum.

#### POST-MORTEM FINDINGS\*

The left pleural cavity contained about 1,000 c.c. of clear, straw-colored fluid. The left lung was firmly adherent to the parietal chest wall. The left upper lobe was

\*Abstract of post-mortem examination performed by Dr. Nathan Mitchell.

occupied by a large mass. The bronchi were traced, and in the region of the left upper lobe bronchus, whitish, firm, opaque tissue, with ulceration of the mucosa, was noted. This tissue extended upward along the course of the left main bronchus, involving the peribronchial and paratracheal tissues. The bronchus was traced upward and it led into a multilocular cavity which contained several ounces of thick, yellowish, creamy pus. Surrounding this cavity and extending into the left lower lobe, diffuse, uniform consolidation of the parenchyma was noted.

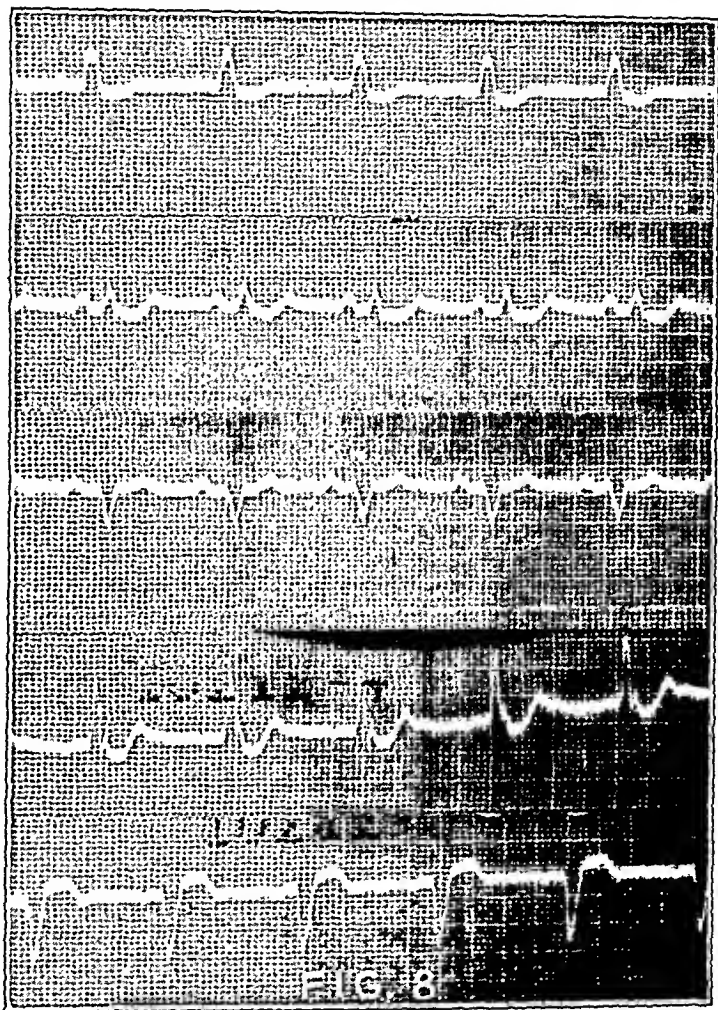


Fig. 8.—Electrocardiogram taken Aug. 28, 1939.

The heart was moderately enlarged. Several white, firm nodules could be seen projecting through the pericardium. On section of the heart, whitish, nodular areas could be seen scattered throughout the myocardium (Fig. 11). These nodules varied from 1 to 4 cm. in diameter and were located in the left ventricular wall and the interventricular septum. There was one large nodule occupying the base of the interventricular septum, extending from the endocardium of the left ventricle through to the endocardium of the right ventricle (Fig. 10), the entire mass being located beneath the right coronary cusp of the aortic valve. The papillary muscles were likewise invaded by the same whitish tissue. The pulmonary arteries and veins were constricted, and the intima was folded by thrombotic, whitish material. The mediastinal lymph nodes were not involved.

The terminal ileum contained a small, hard nodule measuring 3 mm. in diameter. A whitish nodule measuring 1 cm. was seen in the upper pole of the right kidney.



Fig. 9.—Electrocardiogram taken Oct. 16, 1939.

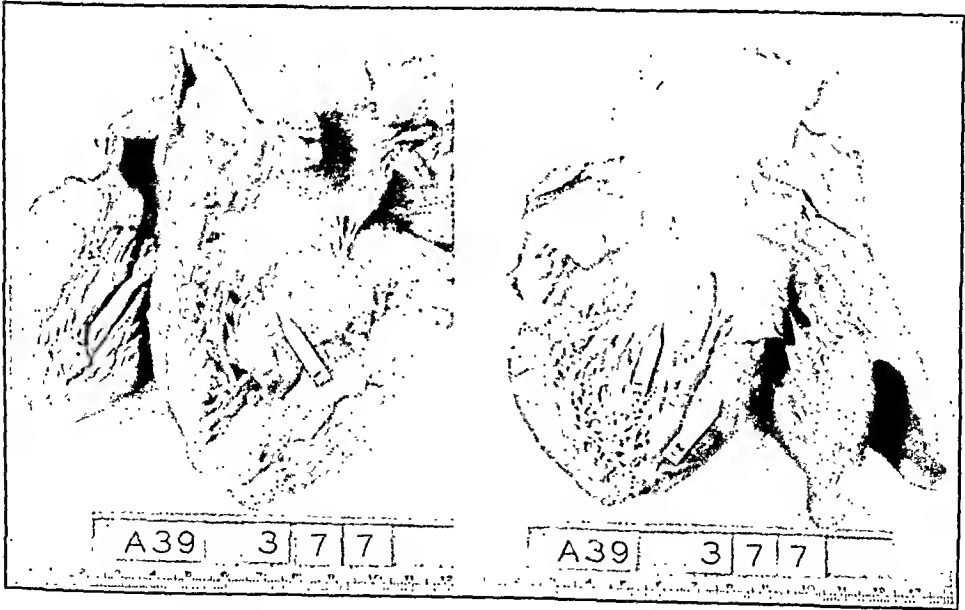


Fig. 10.

Fig. 11.

Near the center of the left kidney, there was a broad, depressed, yellowish, pyramidal-shaped area, well demarcated from the surrounding tissue. The neck of the bladder and the prostatic urethra revealed distortions of the mucosa, and on cut section, the prostate showed many opaque, nodular areas.



Fig. 12.

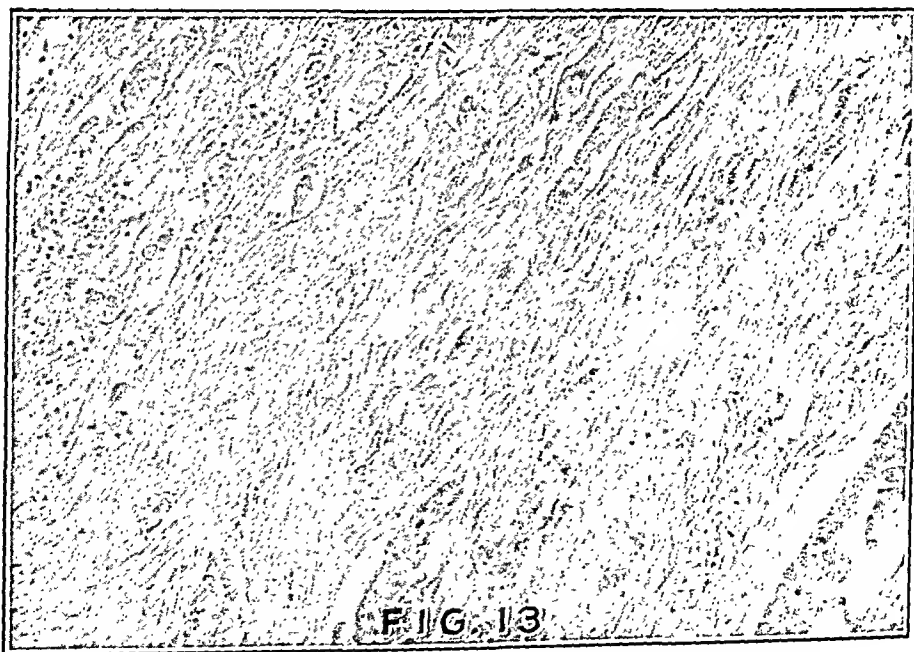


Fig. 13.

Microscopic study disclosed a primary squamous-cell carcinoma with keratinization and necrosis, and deep invasion of the bronchial wall, with ulceration of the mucosa. Lymphatic channel and lymph node invasion and invasion of the pulmonary vessels with tumor thrombosis were found (Fig. 12). Other areas of the lung revealed definite metastatic invasion with permeation of lymphatics and of the alveolar



spaces. The cavity in the left upper lobe showed tumor tissue in its wall and regional chronic pneumonitis. The heart revealed extensive invasion by squamous-cell carcinoma, including tumor thrombi in some of the coronary veins (Fig. 13). The entire region of the base of the interventricular septum, involving the bundle of His and both the right and left branches, disclosed extensive invasion and destruction. The kidney showed an isolated metastatic nodule. The aorta showed limited syphilitic aortitis. The ileum disclosed a small leiomyoma separating the muscle layer and elevating the serosa. The prostate revealed a small, miniature adenocarcinoma, with both chronic and acute prostatitis evident.

#### COMMENT

Most cases of metastatic carcinoma of the heart are associated with primary or secondary intrathoracic tumors. Thus, in Lynburner's series,<sup>14</sup> 88 per cent of the tumors were intrathoracic, and 72 per cent involved the lung. In view of its high incidence, bronchiogenic carcinoma would be of paramount importance in showing a relatively common tendency to invade the heart. This is borne out by the statistics of Scott and Garvin,<sup>4</sup> as previously mentioned.

The case reported herein is of interest for several reasons: In the first place, it afforded a study of the complete clinical course of bronchiogenic carcinoma; and in the second place, it was marked by the presence, during some part of its course, of nearly all of the more common cardiac abnormalities of neoplastic involvement of the heart reported in the literature. Thus, the onset of cardiac symptoms was marked by paroxysmal auricular fibrillation, followed by left bundle branch block and, finally, by complete A-V dissociation with a Stokes-Adams syndrome. These changes in a patient suspected of having malignancy of the lung, in the absence of any other pathologic processes in the heart to explain them, offered important presumptive evidence that the malignant process had invaded that organ. Finally, an opportunity was afforded to check in the human being the clinical findings of conduction system defects with post-mortem findings. It was of interest to determine whether the electrocardiographic finding of left bundle branch block was associated with neoplastic destruction of the left bundle branch, and whether the complete heart block was due to involvement of the bundle of His alone or to simultaneous involvement of both main branches. Unfortunately, post-mortem examination revealed complete destruction of the bundle and its branches, thus rendering impossible morphologic correlation of primary left bundle branch involvement with extension to the right branch during invasion of the entire bundle, as the cause of the complete heart block.

#### SUMMARY

Although metastatic tumors of the heart and pericardium are considered rare, recent studies of autopsy series reported in the literature make it appear that they occur more commonly than is ordinarily believed.



Carcinoma of the bronchus is of paramount importance as a source of secondary tumors of the heart and pericardium.

The clinical features suggestive of a diagnosis of metastatic tumors of the heart are various abnormalities of rhythm, such as heart block, congestive failure, or hemorrhagic or serosanguineous pericardial effusion, each suddenly developing without apparent cause in a patient with known malignancy.

A case of bronchiogenic carcinoma with metastasis to the heart, diagnosed during life, is presented to augment the small group of cases already reported in the literature.

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# CIRCULATORY EFFECTS FOLLOWING THE INTRAVENOUS ADMINISTRATION OF PITRESSIN IN NORMAL PERSONS AND IN PATIENTS WITH HYPERTENSION AND ANGINA PECTORIS

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THIS report deals with some of the cardiovascular reactions observed during the administration of posterior pituitary extract to nine normal persons, to four patients with essential hypertension, and to two with angina pectoris. Previous studies have been concerned chiefly with the effects of large single doses given subcutaneously or intramuscularly. In the present study, pitressin was given intravenously over relatively long periods of time, and the circulatory effects observed suggested certain clinical possibilities.

## METHOD

Pitressin\* (1 c.c. = 20 I. U.) was diluted with normal saline to provide a concentration of 1:1,000, and the rate of flow, during the administration, was controlled and measured by means of an especially prepared burette. Save in the earlier tests, a second burette containing normal saline was included in the circuit in such a manner that a change in flow from saline to pitressin, or vice versa, could be made readily. In most instances, 0.1 c.c./Kg./min. of the pitressin solution was given over a period of from thirty minutes to one hour or more. If this was insufficient to produce severe abdominal cramps, the rate of flow was doubled or tripled. Blood pressures were measured with a mercury sphygmomanometer. Skin temperatures were determined by means of a Tyco's dermaterm. Electrocardiograms were taken with the subject recumbent. Grollman's acetylene method was used in determining the cardiac output.

The person to be tested was allowed to lie quietly for at least thirty minutes while control observations were made in a room with nearly constant temperature. When these observations indicated that a stable state had been reached, the intravenous infusion of saline solution was begun. When the reactions incident to this procedure had disappeared, the change to pitressin solution was made by simply turning a stopcock. Notes were made on the changes in skin color, character of the pulse, and subjective symptoms during the course of the experiment.

## THE EFFECTS: GENERAL CONSIDERATIONS

Almost immediately after the administration of pitressin was started, pallor of the skin and mucous membranes became apparent. The subject appeared ill but felt well. This discrepancy was very striking and sometimes almost unbelievable. The temperature of the skin fell very

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\*Pitressin as prepared commercially by Parke, Davis & Co. was used throughout these experiments.

little during the test period, and, again, a sharp contrast was observed between color and warmth of the skin. The pulse rate did not change significantly, but the amplitude of the radial pulse grew much smaller and, in some subjects, the pulse became difficult to palpate. Despite this obvious arterial constriction, the alterations in blood pressure were small. As a rule, restlessness developed, followed by general malaise and weakness. Sweating always occurred toward the end of the test and was sometimes profuse, interfering with accurate skin temperature determinations.

Abdominal symptoms occurred in every instance, but with wide variations as to time and character of onset. The onset was heralded with nausea, a feeling of weight or a burning sensation in the epigastrium, and borborygmus. Cramplike pains in the lower abdomen usually were followed by bowel urgency; three subjects had a large evacuation immediately following the test.

#### SKIN COLOR

Pallor of the skin developed very rapidly following the injection of pitressin. Pallor was observed when the dilution of pitressin in the blood was calculated to be approximately 1:3,000,000. This is in keeping with the well-known fact that the active principles of the posterior portion of the pituitary gland act in minute doses, smaller than those of any known substance, except perhaps the protein poisons. Sacks<sup>1</sup> has shown this pallor to be the result of the action of posterior pituitary extract on the capillaries and subpapillary venous plexuses, which are the vessels chiefly responsible for skin color.

Affecting the more highly colored portions of the face first, the pallor gradually increased in intensity, involving the entire face, neck, ears, lips, and mucous membranes of the mouth. Later, pallor of the hands, arms, and other portions of the body was observed. The pallor persisted for one and one-half to two hours after the injection of pitressin was stopped.

It is important to point out the rapidity with which changes in skin color occurred as compared with changes in skin temperature. The former were almost immediate and were striking. The latter took place more slowly and were less definite. This adds further confirmation to the work of Sacks in showing that there is only a slight pressor effect, at least in the higher dilutions of pitressin, on the vessels responsible for the warmth of the skin.

#### SKIN TEMPERATURE

Skin temperature determinations were made in sixteen experiments on thirteen subjects. The areas most commonly tested were the forehead and left hypotenar eminence. The usual precautions were observed in so far as possible, but in many tests some factor was present

which vitiated the results. In four tests the conditions were ideal, but the results did not differ significantly from the others. The reason for this probably rested in the fact that the duration of the experiment was rarely over two hours. In general, skin temperature fell slightly, about 1 to 2° F., during the course of the experiment. Exceptionally, the temperature rose a degree or remained at the control level. As emphasized above, even when the pallor was extreme, there was little change in skin temperature. This is in keeping with the observations of Krogh<sup>2</sup> and others who found that in high dilution posterior pituitary extracts have little effect on the size of the arterioles upon which skin temperature is mainly dependent.

#### BLOOD PRESSURE AND PULSE RATE

Oliver and Sehafer,<sup>3</sup> in 1895, observed a rise in blood pressure in anesthetized animals following the intravenous injection of extracts of the pituitary gland. A few years later Howell<sup>4</sup> proved that extracts of the posterior lobe of the gland are responsible for this pressor effect, and this extract became known as vasopressin. Since then, numerous investigators<sup>5</sup> have studied the pressor response of this hormone, both in animals and in man, but reports of its effect on blood pressure have been conflicting. The fact emerges that the blood pressure response

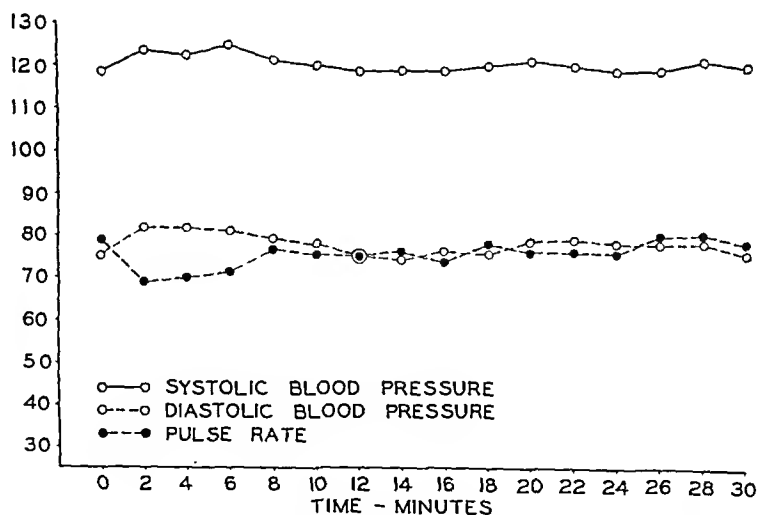


Fig. 1.—Average changes in blood pressure and pulse rate in nine normal persons during intravenous administration of pitressin.

depends on several variable factors, including the amount of the substance given, manner of administration, number of injections, and the presence of other drugs. From a review of published reports, it would appear that in man, moderate amounts of posterior pituitary extract usually do not cause marked changes in blood pressure. A certain tolerance may be established with repeated injections so that the blood pressure response becomes less marked.

Fig. 1 shows the average changes in blood pressure and pulse rate in nine normal persons during the intravenous administration of pitressin. It is readily seen that after a slight initial rise in systolic and diastolic blood pressure, and a slight fall in pulse rate, control values are quickly reached. These changes are probably significant even though slight, because a temporary rise in pressure was observed in each instance. Furthermore, the change from saline to pitressin was made without the subject's being aware of it, and the rise in blood pressure usually occurred before subjective symptoms were apparent. Slight temporary slowing of the pulse rate is probably due to the depressor effect resulting from the increase in blood pressure.

Four patients with essential hypertension were similarly tested, and blood pressure and pulse rate responses of similar magnitude were observed. The only difference was that in the hypertensive subjects, the return of the blood pressure toward the control level occurred more slowly. The changes observed in two patients with angina pectoris were insignificant, but the absence of any fall in blood pressure is of interest because it is thought by some that a fall in blood pressure following posterior pituitary extracts is the result of cardiac weakness resulting from constriction of the coronary vessels.

#### CARDIAC OUTPUT

There has been little study of the alteration in cardiac output in man following the injection of pituitary extracts. Grollman and Geiling<sup>6</sup> made a series of determinations at fifteen-minute intervals on two normal subjects after a single intramuscular injection of posterior pituitary extract. Immediately after administration, they found a slight decrease in cardiac output (average 12 per cent), followed by an increase, and then by a return to the initial level.

TABLE I

NO.	BEFORE PITRESSIN	DURING PITRESSIN	CHANGE IN METABOLIC RATE (%)	CHANGE IN CARDIAC OUTPUT (%)
1	5.11	4.82	-27	-5.1
2	5.92	5.35	-15	-9.6
3	5.03	5.15	-10	+2.4
4	6.08	5.75	-16	-5.0
5	6.43	5.99	± 0	-6.8
6	6.35	5.98	+ 3	-5.8
Average	5.82	5.50	-10.8	-5.0

In our experiments we followed Grollman's technique, except that basal conditions were not observed. The tests were performed in the afternoon; the subject was allowed a small luncheon, and the experiment was begun about one and one-half hours later. Although the food affected the absolute values of the cardiac output, the relative values

were valid because of the short duration of the experiment. Determinations were made just before and during the height of administration of pitressin.

Table I shows the results in the six cases tested. Cardiac output, on the average, was decreased 5.0 per cent. The large decreases in cardiac output observed in animal experiments have been thought by some observers to be due to a direct effect of the drug on the myocardium. In these experiments much larger doses were employed than in the present tests.

#### ELECTROCARDIOGRAMS

Electrocardiograms were taken of six normal subjects before administration of pitressin and at intervals during the administration. No significant changes were observed.

#### PITRESSIN AND ANGINA PECTORIS

The action of posterior pituitary extract on coronary vessels and on the heart is better known for animals than for man. Numerous investigators<sup>7</sup> have shown that this extract causes constriction of the coronary vessels and weakening of the heart in animals. It should be noted, however, that the doses used are usually much greater than the amount normally excreted. It is assumed that posterior pituitary extracts cause constriction of the coronary vessels in man. Kountz and Smith,<sup>8</sup> however, did not observe any significant alteration in coronary flow when pituitary solution was added to the perfusate of a revived dilated human heart. Goldenberg and Rothberger<sup>9</sup> conclude, from their experiments and from a survey of the pertinent literature, that the coronary constrictor action of pitressin provides a means of testing the "spasm theory" of angina pectoris. We thought it would be of interest, therefore, to give pitressin to patients with angina pectoris.

Two patients who had easily provoked anginal pain were selected for testing. Both experienced pain on very small effort or excitement and occasionally even while resting in bed. The tests were carried out in the usual manner, except that the rate of injection of the pitressin was increased more cautiously.

The readings and notes given in abbreviated form in Table II were made while testing Mr. G., a cook, 56 years of age.

After a suitable control period, physiologic saline solution was allowed to run into a vein. The unpleasantness and excitement incident to the introduction of the needle were sufficient to provoke slight but definite substernal discomfort. This quickly passed, and some time later the change was made from saline to pitressin without the subject's knowledge. The solution of pitressin was allowed to run until abdominal cramps became uncomfortable. Anginal pain was not

produced. This same patient on another occasion was given adrenaline, in a dilution of 1:1,000,000, intravenously. Pain resulted very quickly and was preceded only by a slight rise in blood pressure and pulse rate.

TABLE II

TIME	PITRESSIN (C.C./KG./MIN.)	BLOOD PRESSURE		PULSE RATE	REMARKS
		SYSTOLIC	DIASTOLIC		
2.16	0	140	92	88	Comfortable
2.40	0	140	90	84	
2.56	0	142	90	88	
2.57					Injection of saline begun
2.58	0	160	100	100	
3.00	0	158	110	100	Slight substernal pain
3.02	0	148	90	96	Pain less
3.04	0	140	92	96	Pain gone
3.12	0	136	90	86	
3.24	0	132	88	86	
3.28	0	132	90	84	
3.30					Injection of pitressin begun
3.32	0.02	134	90	88	Beginning pallor
3.42	0.02	136	86	80	Pallor marked
3.52	0.04	134	90	80	
4.02	0.10	138	88	78	
4.12	0.12	138	84	80	Cramps
4.18	0.12	138	86	82	Complained of abdominal cramps
4.22	0.12	134	84	80	
4.24					Pitressin solution stopped

TABLE III

TIME	PITRESSIN (C.C./KG./MIN.)	BLOOD PRESSURE		PULSE RATE	REMARKS
		SYSTOLIC	DIASTOLIC		
2.00	0	120	65	68	Face a ruddy color
2.05	0	115	65	68	
2.13	0	115	70	68	
2.20					Saline solution started
2.22	0	112	70	68	
2.27	0	110	65	64	
2.30					Saline stopped; pitressin started
2.32	0.06				Slight pallor
2.34	0.06	120	72	60	Moderate pallor
2.42	0.06	114	72	60	
2.52	0.12				Rate of injection increased
2.55	0.12	118	70	64	Slight abdominal distress; slight sweating; pallor marked
3.04	0.12	112	70	64	Abdominal cramps moderately severe
3.06					Pitressin stopped

A similar test was carried out on Mr. II.,\* aged 58 years, and anginal pain did not occur although sufficient pitressin was given to provoke well-marked abdominal cramps. The notes on the case are given in Table III.

\*This patient has since died, and autopsy revealed an extreme degree of coronary arteriosclerosis.

The above results would seem to point to a curious paradox, in that pitressin, a drug known to cause coronary vasoconstriction, did not provoke pain in anginal patients, while adrenaline, a drug known to cause coronary vasodilatation, readily provoked pain. These facts require explanation. It would appear either that coronary vasoconstriction was not produced with pitressin, or, if it was, that there must have been at least a corresponding decrease in the work of the heart. Experimental evidence points to the fact that pitressin actually does constrict the coronary vessels to a marked degree. Our results show that both the cardiac output is slightly decreased and the metabolic rate is lowered by an average of 10.8 per cent. Accordingly, it would seem that the decrease in coronary flow was compensated for by the decrease in the work of the heart. An interesting parallel is seen in the case of adrenaline. This drug may quickly provoke pain in anginal patients although it causes coronary vasodilatation. The explanation lies in the fact that the work of the heart is increased to a greater extent than is the coronary flow.

Katz and Lindner<sup>10</sup> point out that "for practical purposes the important thing is not whether the substance has a coronary vasodilator or vasoconstrictor action nor whether the substance increases coronary flow or decreases it but rather how it influences the relation of the change in coronary flow to the alteration in the work of the heart and to the energy cost on the part of the heart doing this work." On this basis, we may conclude, therefore, that pitressin in amounts sufficient to provoke distressing abdominal cramps does not significantly decrease the blood supply to the myocardium in relation to the work of the heart and that it is safe and practical to give pitressin to patients with coronary heart disease.

#### DISCUSSION

It is clearly apparent from these results that pitressin, given in the manner described above, has a cumulative effect in that a point of tolerance is reached. The limiting symptoms are related to the gastrointestinal tract, and these may be pronounced if enough of the drug is given. These symptoms include nausea, vomiting, and abdominal cramps, sometimes followed by evacuation of the bowel. There was not a single instance of significant cardiovascular symptoms in either normal persons or cardiac patients. There was evidence of constriction of the minute vessels and capillaries of the skin and of the large arteries; there was little effect on the arterioles, judging by the minor alterations in blood pressure and skin temperature. Furthermore, there was no evidence that the heart was adversely affected. The cardiac output was slightly decreased, and the metabolic rate was lowered. Pain was not produced in patients with severe coronary arteriosclerosis who were subject to easily induced attacks of angina pectoris.



In contrast to the above, severe symptoms have been reported following large single injections of posterior pituitary extract. These include cyanosis, shallow respirations, sweating, palpitation, faintness, feeling of heat, and abdominal cramps. Sometimes these symptoms are severe and alarming, and convulsions have been observed. These symptoms may be accompanied by considerable rises in blood pressure and other evidence of vasoconstriction. For these reasons and because of the known coronary vasoconstrictor action in animals, there has been a natural hesitancy to use posterior pituitary extracts in certain patients, especially those with heart disease.

Our experience suggests that pitressin may be slowly injected intravenously in amounts sufficient to produce marked gastrointestinal symptoms without producing alarming or even significant circulatory symptoms. This is true for normal persons and for patients with hypertensive or coronary heart disease. By the same technique it is possible that in pregnancy or in the treatment of ileus the desired therapeutic effect could be produced without fear of untoward circulatory symptoms.

#### SUMMARY AND CONCLUSIONS

A dilute solution of pitressin given by intravenous infusion has a cumulative effect.

Nine normal persons, four patients with essential hypertension, and two patients with coronary heart disease were given a dilute solution of pitressin intravenously over a period of from thirty minutes to one hour or more.

Gradually developing gastrointestinal symptoms limited the amount which could be given.

Significant cardiovascular symptoms were observed neither in the normal persons nor in the patients with heart disease. There was evidence of marked constriction of the minute vessels and of the large arteries, but not of the arterioles. There were only slight changes in the pulse rate, blood pressure, metabolic rate, and cardiac output.

Anginal pain was not reproduced in two patients with severe coronary heart disease who received sufficient pitressin to cause uncomfortable abdominal cramps. A minute amount of adrenaline when given to one of these patients produced anginal pain. It is suggested that in certain respects pitressin and adrenaline act in an opposite manner; the former causes coronary vasoconstriction but a decrease in the work of the heart, while the latter causes coronary vasodilation but an increase in the work of the heart.

Following the procedure used in these tests, pitressin, in therapeutic amounts, may be given without fear of untoward cardiovascular effects.

We should like to express our thanks to Dr. Paul D. White, in whose laboratory this work was carried out, for his interest and advice.

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## EFFECT OF SHORT-WAVE DIATHERMY ON THE CUTANEOUS TEMPERATURES OF THE FEET

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THE primary value of heat in the treatment of peripheral vascular disease lies in its ability to produce peripheral vasodilation.<sup>1</sup> However, local heat is capable of doing more harm than good.<sup>1-3</sup> It is known that short-wave diathermy causes more or less deep through-and-through heating of the bodily region to which it is applied, and is thus more efficient than the ordinary methods of heating by conduction or infrared irradiation. However, it is our opinion that, when arterial insufficiency is present, local application of short-wave diathermy is contraindicated fully as much as is any other form of local application of heat, and that the contraindications far outweigh any advantages the method might have.

The contraindications to the employment of heat locally, plus recognition of the fact that the primary value of heat lies in its ability to cause vasodilation, suggest the advisability of inducing peripheral vasodilation by the application of heat over remote regions of the body which are unaffected by the lesions of peripheral vascular disease. That general peripheral vasodilation may follow application of heat to a region remote from the affected extremity has been demonstrated by many investigators.<sup>4-10</sup> Because of the deep through-and-through heating of a region of the body when short-wave diathermy is used, this method should be ideally adapted to produce peripheral vasodilation by remote heating of the tissues. It is realized that temperatures of the skin may not indicate the temperatures of the deeper tissues, but such temperatures are thought to indicate, at least, the arteriolar activity of the skin, so important in peripheral vascular disease.<sup>11</sup>

Without discussing the many controversial reports regarding so-called specific effects of short-wave diathermy on the peripheral capillaries, we believe that no conclusive experiments have been brought forward to indicate the existence of any such specific effect, whether it be vasoconstricting or vasodilating. We are inclined to agree with Weisz and associates,<sup>12</sup> who, after scientific experimental work, found no effect of short-wave diathermy on the capillaries of a frog's tongue which could not be explained on a purely thermal basis. One of us (Krusen<sup>13</sup>), in a

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survey of the literature, found that in the light of knowledge in the field of short-wave diathermy then existing, the effects could be explained only on the basis of the heating which was produced.

#### TECHNIQUE

The apparatus for measuring the skin temperature which we used in the following observations was the cutaneous thermocouple described by Eddy and Taylor.<sup>14</sup> The continuous application of multiple thermocouples was tried, but it was found that short-wave current, even so remotely applied, caused the thermocouples to heat beyond the actual temperature of the skin. Therefore, the portable cutaneous thermocouple was used, and all readings were recorded with the diathermy current turned off. It was found that maximal temperature of the skin was not indicated by the thermocouple until after the current had been turned off for one-half to one minute; that is, the temperature indicated by the thermocouple applied immediately after the current was turned off was from 0.5 to 1.5° C. lower than the temperature indicated when the thermocouple was applied from thirty seconds to one minute later. No scientific explanation of this phenomenon can be offered at present. No such delay in maximal reading was noted following other methods of warming the body.

The observations which we made were carried on in a room in which the temperature was manually controlled. This room could easily be maintained at a constant temperature for the three hours required to conduct each observation. The temperature of the air in the room was most frequently kept at 78° F. (25.5° C.), although occasionally it was maintained at 74 or 76° F. (23.3 or 24.2° C.). Sheard and associates<sup>15</sup> found that this range of temperature is somewhat below the environmental temperature at which the peripheral vessels dilate, and thus permits proper evaluation of the various methods of vasodilation used. Another equally important reason for maintaining a range of temperature of 74 to 78° F. (23.3 to 25.5° C.) is that many of the subjects employed were rather debilitated persons who would have been uncomfortable in the supine position with only a sheet or turkish towel over the chest, trunk, and thighs, at a temperature below this range.

An attempt was made to stabilize the temperatures of the skin of the extremities by withholding the meal prior to each observation. To this end, the subject lay supine with feet, head, and arms uncovered, in a room maintained at constant temperature for one-half to one hour, or until three consecutive readings of the skin temperature over the plantar surface of the first and third toes and over the dorsum of each foot had been recorded.

Various applications of short-wave diathermy suggested themselves, and the following methods were tried:

1. Four turns of diathermy cable were wrapped around the thigh of the normal, or the less severely involved, extremity.
2. This same application was made over the thigh of the involved limb.

3. The cable was applied over the lower portion of the abdomen in the form of an involute coil of four turns (a so-called pancake coil).

4. The cable in this same "pancake" form was placed under the lumbosacral region of the subject.

5. The pad and cuff technique was employed. A pad measuring 4 by 6 inches (10 by 15 cm.) was placed under the lumbosacral region, and a cuff measuring 3 by 12 inches (8 by 30 cm.) was applied around the middle third of the normal or less severely involved limb.

6. The same method as that last mentioned (5) was employed, except that the cuff was applied around the involved limb.

7. Pads measuring 4 by 6 inches (10 by 15 cm.) were applied for through-and-through treatment of the lower abdomen. That is, one pad was placed over the lower portion of the abdomen and the other one was placed under the lumbosacral region.

In all the above applications, the electrodes used were spaced at least 1 inch (2.5 cm.) from the skin by turkish toweling. This was done so that a maximal deep heating of tissue with minimal heating of the skin would be obtained. It is a well-known fact, demonstrated on living tissue by various investigators, that the greater the distance of spacing between the skin and the electrode, the more uniform is the deep heating of tissue.<sup>12, 13</sup>

After using the various applications previously mentioned and comparing one with the other, several points became evident. So far as the degree of resultant vasodilation which was produced is concerned, all the methods appeared to be suitable and their effects were comparable. In this regard, no one method seemed to have any advantage over others. However, in the matter of technique of application and comfort of the patient, several methods had rather marked disadvantages. It is a tedious procedure to apply the cable around the thigh, and rarely can this application be left during the entire hour of heating without the development of "hot spots." These chiefly occur where the weight of the limb exerts pressure on the turns of cable passing under it.

For those not fully acquainted with the application of short-wave diathermy, it is to be noted that a mechanical means of determining the exact amount of short-wave radiation introduced into the patient is not available at the present time, so that it is necessary to rely entirely on the subjects' sensation of "comfortable heat" for determination of dosage. Admittedly, this method of determining dosage is far from satisfactory, since personal interpretation of "comfortable heat" varies greatly. However, this disadvantage is common to all short-wave diathermy applications. It was minimized, so far as these studies were concerned, by using the same diathermy apparatus and identical applications on each patient. The approximate meter reading to be used can be determined best by employing a reliable assistant to act as a subject. This meter reading can be used on each patient with but small variation.

When it was ascertained that no one of the applications previously mentioned proved itself superior in its ability to promote peripheral

vasodilation, it was decided to use constantly that method which had presented the least technical difficulties. This was found to be the application of the cable in "pancake" formation under the lumbosacral region. This application was further modified by placing the cable under a mattress approximately 11½ inches (4 cm.) in thickness, similar in construction to the kapok or hair-filled, rubberized fabric-covered mattress used in the short-wave diathermy cabinets for induction of fever. This method proved highly satisfactory, since it provided nearly uniform application with a minimum of discomfort to the patients.

#### RESULTS OF OBSERVATIONS

Twenty observations (Table I) were made on eleven normal persons. In eighteen of these observations the temperature of the skin of the plantar surface of the right and left first toes increased to between 33.0 and 35.5° C. during one hour of irradiation with short-wave diathermy. In the remaining two observations, both of which concerned the same person, the temperature of the toes increased only to values between 28.0 and 30.5° C. The oral temperature varied from no change in one observation to an increase of 1.2° F. in two others.\* The average change in all observations was an increase of 0.6° F. (0.33° C.).

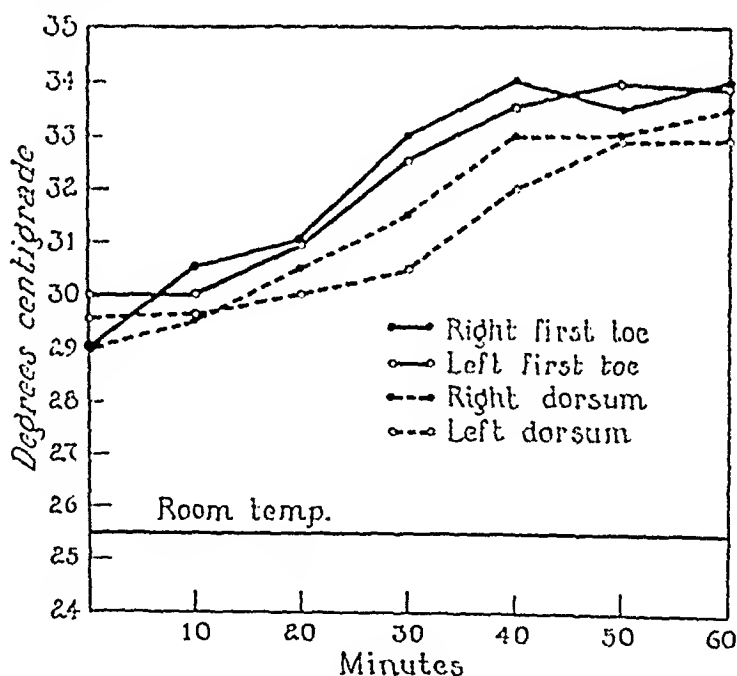


Fig. 1.—Changes in temperature occurring during observation 13 (Table I) on a normal subject, after sixty minutes of application of heat.

Fig. 1 (observation 13, Table I) shows the changes in temperature of the skin in a typical observation of this series. The temperature of the first toes increased to approximately 34.0° C. in about forty minutes,

\*Because in this country physicians usually think of oral temperatures in terms of the Fahrenheit scale, the oral temperatures are recorded in Fahrenheit degrees rather than in centigrade degrees.

TABLE I

CHANGES IN TEMPERATURE IN THE SKIN OF THE TOES AND FEET, AND OF THE MOUTH: TWENTY OBSERVATIONS ON ELEVEN NORMAL SUBJECTS AFTER ONE HOUR OF SHORT-WAVE DIATHERMY

OBSERVATION	AGE (YR.) AND SEX OF PATIENT	MODE OF APPLICATION OF DIATHERMY	FIRST TOE, PLANTAR SURFACE (°C.)						DORSUM OF FOOT (°C.)						ORAL TEMPERATURE				ROOM TEMPERATURE (°C.)
			RIGHT			LEFT			RIGHT			LEFT			° F.				
			AT REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE		
1	36, M	Pads over and under abdomen	29.5	34.5	+5.0	29.0	35.0	+5.0	30.5	34.0	+3.5	30.0	34.5	+4.5	98.2	98.8	+0.6	25.5	
2	36, M	Pads over and under abdomen	27.0	35.0	+8.0	26.5	35.5	+9.0	29.0	35.0	+6.0	27.5	35.5	+8.0	97.8	98.6	+0.8	25.0	
3	38, M	Pads over and under abdomen	25.5	33.0	+7.5	27.0	33.0	+6.0	29.5	35.0	+5.5	28.5	32.0	+3.5	97.4	98.4	+1.0	25.5	
4	26, M	Pads under back; cuff around right thigh	23.0	33.0	+10.0	22.5	33.0	+10.5	26.0	33.0	+6.5	27.0	33.5	+6.5	98.2	99.0	+0.8	25.5	
5	38, M	Pads under back; cuff around right thigh	27.5	29.5	+2.0	27.5	28.0	+0.5	29.0	29.5	+0.5	30.0	29.5	-0.5	97.4	97.6	+0.2	25.0	
6	28, M	Cable under mattress	25.5	33.5	+8.0	30.0	34.0	+4.0	27.0	33.0	+6.0	30.5	33.5	+3.0	98.0	98.4	0.4	25.5	
7	38, M	Cable under mattress	27.0	30.5	+3.5	27.5	30.5	+3.0	28.0	30.0	+2.0	28.0	30.0	+2.0	98.0	98.4	+0.4	25.5	
8	36, M	Cable under mattress	25.0	33.5	+8.5	24.5	34.0	+9.5	27.0	32.0	+5.0	26.5	31.5	+5.0	97.4	98.6	+1.2	25.5	
9	32, M	Cable under mattress	27.5	34.0	+6.5	27.5	35.5	+8.0	28.5	35.5	+7.0	29.0	35.5	+6.5	98.2	99.4	+1.2	25.5	
10	36, M	Cable under mattress	30.0	34.0	+4.0	29.5	33.5	+4.0	30.5	33.5	+3.0	30.5	33.5	+3.0	97.8	98.4	+0.8	25.5	
11	36, M	Cable under mattress	25.0	34.0	+9.0	25.0	34.0	+9.0	29.5	33.0	+3.5	29.5	32.5	+3.0	98.8	98.8	0.0	25.5	
12	36, M	Cable under mattress	26.0	33.5	+7.5	26.0	34.0	+8.0	27.5	33.5	+6.0	27.0	33.5	+6.5	98.0	98.2	+0.2	25.5	
13	28, M	Cable under mattress	29.0	34.0	+5.0	29.0	34.5	+5.5	29.0	33.5	+4.5	29.5	33.0	+3.5	98.0	98.4	+0.4	25.5	
14	27, M	Cable under mattress	26.0	34.0	+8.0	26.0	34.5	+8.5	27.5	33.5	+6.0	27.5	33.0	+5.5	98.4	98.6	+0.4	25.5	
15	34, M	Cable under mattress	25.0	34.5	+9.5	24.5	34.5	+10.0	28.0	32.0	+4.0	27.5	33.0	+5.5	98.2	98.4	0.0	25.5	
16	34, M	Cable under mattress	28.0	35.0	+10.5	24.5	35.0	+10.5	28.0	33.8	+5.8	28.0	33.5	+5.5	98.6	99.0	+0.4	25.5	
17	34, M	Cable under mattress	24.5	34.5	+6.5	28.5	34.5	+6.0	27.5	33.5	+6.0	27.5	34.0	+6.5	98.2	99.0	+0.8	25.0	
18	28, M	Cable under mattress	26.0	34.5	+8.5	25.5	35.0	+9.5	30.0	34.0	+4.0	29.0	34.0	+5.0	98.0	99.0	+1.0	28.0	
19	27, M	Cable under mattress	25.5	34.0	+8.5	24.5	34.0	+9.5	28.0	33.0	+5.0	30.5	33.5	+3.0	98.6	99.0	+0.4	25.0	
20	29, M	Cable under mattress	29.0	34.5	+5.5	28.0	34.5	+6.5	30.0	35.0	+5.0	29.5	35.0	+5.5	98.2	98.4	+0.2	25.5	

with the temperature of the dorsum of the feet lagging behind 1.0 to 1.5° C. The curve ascends sharply during the first ten minutes, indicating a prompt peripheral vasodilating response. This result is in marked contrast to the first ten-minute change seen in determinations made on patients who have organic arterial occlusive disease, in observations of whom no change may be discovered. The rate of increase, however, cannot be considered as characteristic, since it will be modified greatly with different resting temperatures. Thus, in a normal patient with a resting skin temperature of the toes of 30.0° C., the temperature may increase only 0.5° C. in the first ten minutes of irradiation.

The seven studies made of five patients who had essential hypertension (grades 2 to 3) were similar in results to those of normal subjects (Table II). The rate and intensity of the increase in temperature of the skin seemed in no way to be characteristic.

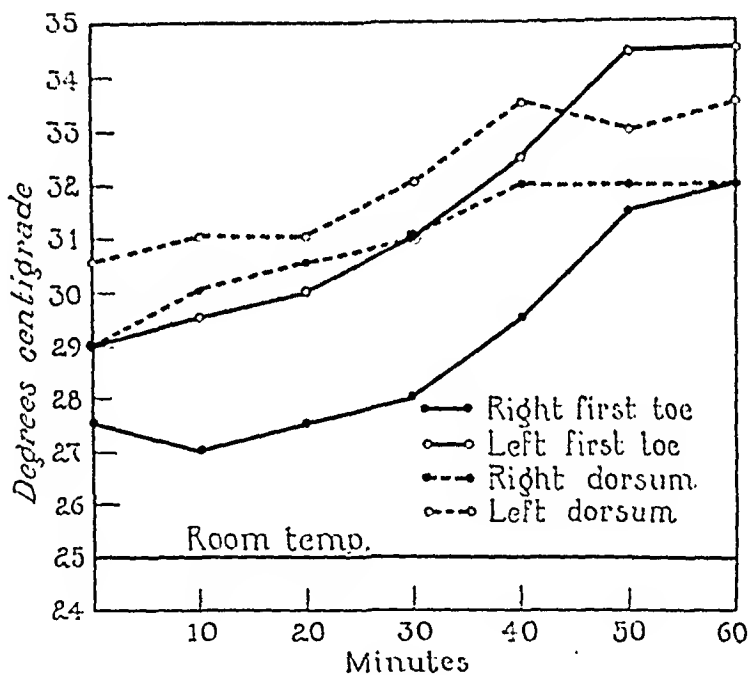


Fig. 2.—Changes in temperature occurring in observation 9 (Table III), after sixty minutes of application of heat. The patient was suffering from arteriosclerosis obliterans.

Eighteen observations were made on thirteen patients who had arteriosclerosis obliterans (Table III). The temperature of the skin of both first toes of twelve of these patients increased. The temperature of the left first toe of one patient remained unchanged. The mode rise was to a maximum of 31.5° C. The average increase in oral temperature was 0.65° F.

Fig. 2 (observation 9, Table III) reveals a slow change in temperature reaching its maximal height in fifty to sixty minutes. The temperature of the left first toe increased slowly to a normal value, but the tempera-



TABLE II  
CHANGES IN TEMPERATURE OF THE SKIN OF THE TOES AND FEET, AND OF THE MOUTH: SEVEN OBSERVATIONS ON FIVE PATIENTS SUFFERING FROM ESSENTIAL HYPERTENSION

OBSERVATION	GRADE OF ESSENTIAL HYPERTENSION	AGE (YR.) AND SEX OF PATIENT	MODE OF APPLICATION OF DIATHERMY	FIRST TOE, PLANTAR SURFACE (°C.)						DORSUM OF FOOT (°C.)						ORAL TEMPERATURE (°F.)			ROOM TEMPERATURE (°C.)
				RIGHT			LEFT			RIGHT			LEFT			REST	AFTER DIATHERMY	CHANGE	
				REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE				
1	2+	36, F	Cable under mattress	27.5	35.0	+7.5	27.5	35.5	+8.0	31.5	35.0	+4.5	31.5	35.0	+4.5	97.4	99.0	+1.6	25.5
2	3	30, M	Cable under mattress	28.5	33.0	+4.5	27.5	33.0	+4.5	30.5	32.0	+1.5	31.5	32.0	+0.5	98.6	99.0	+0.4	25.0
3	3	35, M	Cable under mattress	25.5	33.0	+7.5	25.5	33.0	+7.5	28.0	32.0	+4.0	27.5	32.0	+4.5	97.4	98.4	+1.0	25.0
4	3	35, M	Cable under mattress	28.5	34.0	+5.5	28.5	34.0	+5.5	30.0	32.5	+2.5	30.0	32.5	+2.5	97.8	99.0	+1.2	25.0
5	2+	40, M	Cable under mattress	26.0	33.5	+7.5	25.5	34.5	+9.0	28.5	32.0	+3.5	30.5	33.5	+3.0	99.0	99.4	+0.4	25.0
6	2	39, M	Cable under mattress	26.0	34.5	+8.5	26.5	34.5	+8.0	29.0	33.5	+4.5	29.0	33.0	+4.0	98.0	98.8	+0.8	25.5
7	2+	36, F	Cable around left thigh	30.5	33.5	+3.0	30.5	34.0	+3.5	31.0	34.0	+3.0	31.0	34.5	+3.5	97.6	98.4	+0.8	25.5

TABLE III  
CHANGES IN TEMPERATURE OF THE SKIN OF THE TOES AND FEET, AND OF THE MOUTH: EIGHTEEN OBSERVATIONS ON THIRTEEN PATIENTS  
SUFFERING FROM ARTERIO-SCLEROSIS OBLITERANS

OBSERVATION	AGE (YR.) AND SEX OF PATIENT	MODE OF APPLICATION OF DIATHERMY	FIRST TOE, PLANTAR SURFACE (°C.)						DORSUM OF FOOT (°C.)						ORAL TEMPERATURE (°F.)			ROOM TEMPERATURE, (°C.)
			RIGHT			LEFT			RIGHT			LEFT			REST	AFTER DIATHERMY	CHANGE	
			REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE				
1	64, M	Cable under mattress	30.0	32.0	+2.0	30.0	30.0	0.0	30.0	32.5	+2.5	31.5	33.0	+0.5	98.6	98.8	+0.2	26.0
2	58, M	Cable under mattress	25.0	30.0	+4.0	25.0	29.5	+4.5	27.0	29.5	+2.5	27.5	29.5	+2.0	98.4	99.0	+0.6	25.5
3	51, M	Cable under mattress	Amputated			31.0	32.0	+1.0	Amputated			32.5	33.5	+1.0	98.4	98.6	+0.2	25.5
4	51, M	Cable under mattress	Amputated			29.0	31.0	+2.0	Amputated			30.5	32.5	+2.0	97.8	98.2	+0.4	25.5
5	45, M	Cable under mattress	28.5	32.0	+3.5	31.5	34.0	+2.5	31.5	33.5	+2.0	33.0	35.0	+2.0	98.2	98.6	+0.4	25.0
6	65, M	Cable under mattress	28.5	31.0	+2.5	27.0	29.0	+2.0	30.5	32.0	+1.5	30.0	31.0	+1.0	98.0	99.0	+1.0	25.0
7	65, M	Cable under mattress	27.0	31.5	+4.5	27.5	29.5	+2.0	30.0	31.0	+1.0	29.5	30.5	+1.0	97.4	98.4	+1.0	25.0
8	61, M	Cable under mattress	26.5	30.5	+4.0	28.5	34.5	+6.0	29.5	32.5	+3.0	30.5	34.0	+3.5	98.6	99.0	+0.4	25.0
9	61, M	Cable under mattress	27.5	32.0	+4.5	29.0	34.5	+5.5	29.0	32.0	+3.0	30.5	33.5	+3.0	98.4	98.8	+0.4	25.0
10	62, F	Cable under mattress	29.0	32.0	+3.0	29.5	32.0	+2.5	30.0	30.5	+0.5	29.5	31.5	+2.0	98.6	98.8	+0.2	25.0
11	66, M	Pad under back; Cuff on right thigh	28.0	31.0	+3.0	29.0	32.5	+3.5	31.0	31.0	0.0	31.0	32.0	+1.0	98.8	98.8	+0.0	25.0
12	51, M	Pads over and under abdomen	Amputated			29.5	31.5	+2.0	Amputated			30.0	33.5	+3.5	98.2	98.8	+0.6	25.5
13	40, M	Cable around right thigh	25.0	27.0	+2.0	27.5	31.5	+4.0	28.0	31.5	+3.5	29.0	33.0	+4.0	98.2	98.8	+0.6	25.5
14	60, M	Cable around right thigh	30.5	33.5	+3.0	27.0	29.5	+2.5	29.0	31.0	+2.0	30.5	34.0	+3.5	98.2	98.8	+0.6	25.5
15	52, M	Cable around right thigh	29.5	32.0	+2.5	29.0	32.5	+3.5	30.0	33.0	+3.0	29.5	33.5	+4.0	97.8	99.0	+1.2	25.5
16	60, M	Cable around left thigh	28.5	33.0	+4.5	27.0	30.0	+3.0	29.0	30.5	+1.5	29.5	34.5	+5.0	98.0	98.8	+0.8	25.5
17	52, M	Cable around left thigh	25.0	30.5	+5.5	23.0	28.5	+5.5	29.0	31.5	+2.5	24.5	28.5	+4.0	97.4	98.4	+1.0	25.0
18	48, M	Cable around left thigh	29.0	31.5	+2.5	30.5	32.5	+2.0	30.0	32.5	+2.5	31.5	33.0	+1.5	97.4	99.2	+1.8	25.0

ture of the right toe lagged to the extent of  $2.5^{\circ}\text{C}$ . at the end of sixty minutes. The indications of this curve correspond to the clinical findings in this case. The patient was admitted to the Mayo Clinic two weeks prior to the making of the observations, suffering from acute occlusion of the right popliteal artery. The foot had responded well, but slowly, to routine conservative measures.

Thirteen observations were performed on nine patients who had thrombo-angiitis obliterans (Table IV). The temperatures of the skin of the first toes were increased over the resting values in all cases. In several instances the skin temperature rose to  $31.5^{\circ}\text{C}$ ., with a secondary rise to  $34.0^{\circ}\text{C}$ . The increase in oral temperature averaged  $0.7^{\circ}\text{F}$ .

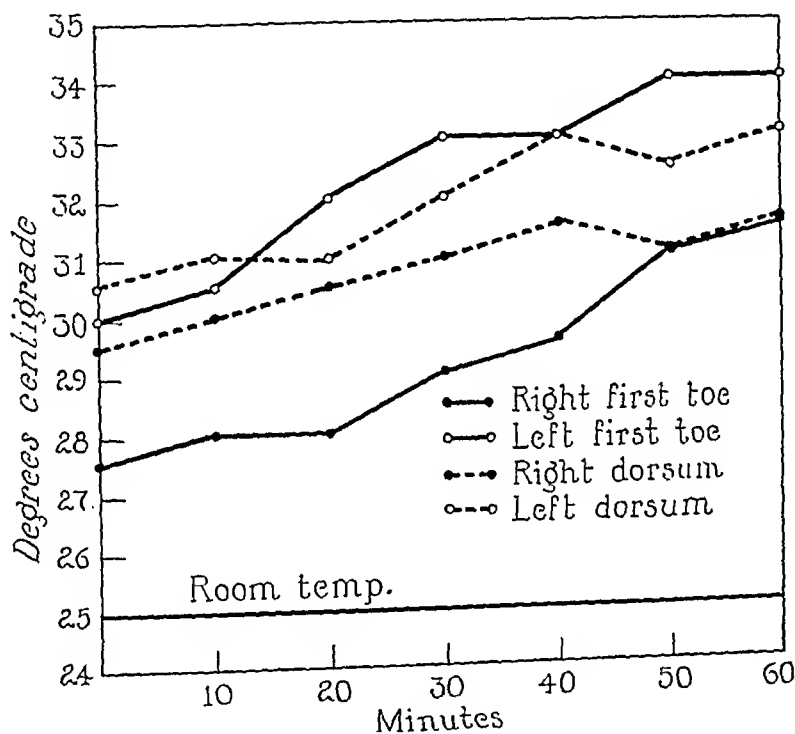


Fig. 3.—Changes in temperature occurring in observation 8 (Table IV) after sixty minutes of application of heat on a patient suffering from thromboangiitis obliterans.

Fig. 3 (observation 8, Table IV) indicates the changes in temperature of the skin in a typical observation in this series. The left foot reacted in such a manner that the curve could not be distinguished from a curve in our normal series. The temperature of the right first toe increased very slowly, whereas the dorsum of that foot reacted in a more nearly normal manner.

An attempt was made to learn whether short-wave diathermy would bring about a higher temperature of the feet than could be produced by the several other methods mentioned in both the literature and in the first part of this paper. Ten such studies were carried out; in eight of these diathermy succeeded, and in two it preceded the other methods of warming. In six of the ten instances one upper extremity of the subject was immersed to the midportion in a large tub of water which was

TABLE IV

CHANGES IN TEMPERATURE OF THE SKIN OF THE TOES AND FEET, AND OF THE MOUTH: THIRTEEN OBSERVATIONS ON NINE PATIENTS SUFFERING FROM THROMBOANGITIS OBLITERANS

OBSERVATION	AGE (YR.) AND SEX OF PATIENT	MODE OF APPLICATION OF DIATHERMY	FIRST TOE, PLANTAR SURFACE (°C.)						DORSUM OF FOOT (°C.)						ORAL TEMPERATURE (°F.)			ROOM TEMPERATURE, (°C.)
			RIGHT			LEFT			RIGHT			LEFT			REST	AFTER DIATHERMY	CHANGE	
			REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE	REST	AFTER DIATHERMY	CHANGE							
1	45, M	Cable under mattress	28.5	31.5	+3.0	29.5	31.5	+2.0	30.0	31.5	+1.5	30.5	31.5	+1.0	98.6	99.2	0.6	25.5
2	31, M	Cable under mattress	31.0	34.0	+3.0	31.5	34.0	+3.5	31.0	32.5	+1.5	31.5	33.0	+1.5	97.6	98.2	+0.6	25.5
3	54, M	Cable under mattress	33.0	35.0	+2.0	30.0	31.5	+1.5	33.5	35.0	+1.5	31.5	33.0	+1.5	97.8	98.6	+0.8	25.5
4	32, M	Cable under mattress	31.0	34.5	+3.5	30.5	32.0	+1.5	31.5	33.5	+2.0	31.0	31.0	0.0	97.2	98.2	+1.0	25.5
5	36, M	Cable under mattress	26.5	29.5	+3.0	27.5	31.0	+3.5	28.5	29.0	+0.5	29.5	31.0	+1.5	98.2	98.6	+0.4	25.5
6	40, M	Cable under mattress	29.0	31.5	+1.5	Amputated	Amputated		30.5	32.5	+2.0	Amputated	Amputated		98.8	99.2	+0.4	25.5
7	52, M	Cable under mattress	27.5	31.5	+4.0	29.0	33.0	+4.0	Amputated	Amputated		29.5	34.0	+4.5	97.6	98.6	+1.0	30.0
8	50, M	Cable under mattress	28.5	31.5	+3.0	30.0	34.0	+4.0	29.5	31.5	+2.0	30.5	33.0	+2.5	98.0	98.4	+0.5	25.0
9	32, M	Cable under mattress	28.5	31.5	+3.0	26.0	30.0	+4.0	28.5	31.0	+2.5	28.0	32.0	+4.0	97.8	98.8	+1.0	25.0
10	32, M	Cable under mattress	27.0	32.0	+5.0	26.0	30.5	+4.5	29.0	31.0	+2.0	29.0	32.0	+3.0	98.0	98.4	+0.4	25.0
11	32, M	Pads over and under abdomen	32.0	34.0	+2.0	31.0	31.5	+0.5	32.0	32.0	0.0	31.5	31.5	0.0	98.2	98.8	+0.6	25.5
12	36, M	Pads over and under abdomen	27.5	29.0	+1.5	28.5	30.5	+2.0	30.0	30.0	0.0	30.5	31.0	+0.5	98.0	98.8	+0.8	25.5
13	45, M	Pad under back; Cuff on right thigh	27.5	32.5	+5.0	29.5	32.5	+3.0	29.5	32.0	+2.5	30.0	32.5	+2.5	98.4	99.2	+0.8	25.5

maintained at a temperature of between 112 and 115° F. (44.4 and 46.1° C.). An infrared luminous baker was applied to one upper extremity of each of two other subjects, and the luminous infrared source was applied to the lower portion of the abdomen of each of the remaining two. As has been said, in eight of these ten instances short-wave diathermy was applied immediately following one hour of this comparison heating. In each of these cases, following application of diathermy, there was an additional rise in skin temperature ranging from

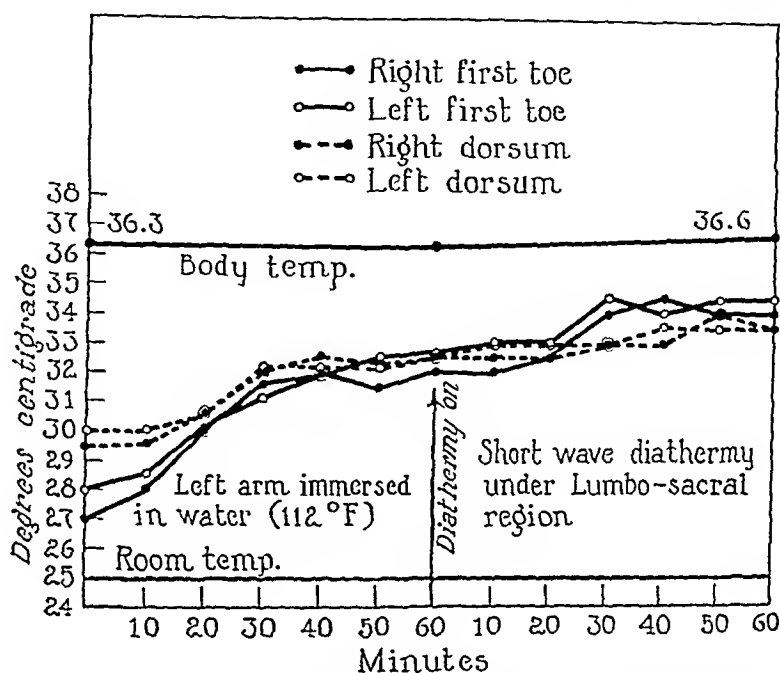


Fig. 4.—Comparative changes in temperature obtained by immersion of left arm of a subject for sixty minutes in water of 112° F. (44.4° C.) temperature, and by subsequent application of short-wave diathermy for sixty minutes under the lumbosacral region.

0.5 to 7.0° C. The average additional rise was 3.1° C. In the remaining two of the ten instances, as was said above, the comparison warming was effected immediately following one hour of application of diathermy. This resulted in a fall in skin temperature during the warming period, which averaged 2.5° C. Fig. 4 represents a typical observation in this series. We realize that the arrangement employed cannot be considered to have furnished a scientific comparison because we have no way of determining the intensity of heat induced by diathermy. Further, in all cases the systemic (oral) temperature was elevated by short-wave diathermy, whereas control methods brought about no appreciable change.

#### COMMENT

When the observations reported in this paper were started, we had some hope that the changes in rate and intensity of the temperature of the skin during application of short-wave diathermy might prove to be of prognostic, or even of diagnostic, value. We thought it might be

possible that a graph of a standard, closely controlled study might be "read" as a guide to diagnosis and prognosis. However, it soon became evident that too many variables existed to expect consistent response even from the clinically normal patient. We realized from the first that we would be unable to apply high frequency current to each patient with identical intensity, because of the present inability to measure the amount of heat actually given to the patient. An identical cable electrode apparatus would minimize this particular variable, but differences in thickness and consistency of subcutaneous tissue introduce further variable factors. However, such variability is minor, when compared with the inherent difference in vascular response seen in studies of clinically normal subjects. Observations 5 and 7, Table I, illustrate this point well. In these observations on the same subject, the temperature of the skin failed to increase appreciably during the hour of irradiation. The subject was a tall, thin person whose chief reason for coming to the clinic was coldness of the feet. Years before, he had sustained a compound fracture of the lower third of the left tibia and fibula, which had healed with some deformity and narrowing of the leg in that region. The arterial supply and venous return appeared to be normal and no clinical vascular differences existed between the two limbs. No explanation for this man's failure to respond to the diathermy heating can be offered. Several investigators<sup>5, 16-18</sup> have reported instances in which peripheral vasodilation in the lower extremities of normal persons failed to occur following warming of an upper extremity. In retrospect, we believe that had this subject's bodily temperature been elevated a degree or so higher, the peripheral capillaries might suddenly have been released of their constriction.

To obtain comparable records it also would be necessary that each subject's skin temperature be at the same value when application of short-wave diathermy is begun. We made no attempt to do this, partly because we did not wish to cool unduly the extremities of patients who had organic vascular disease, and also because the ultimate height of temperature is far more important than the number of degrees of change in temperature.

It is of therapeutic value to know how long the increase in oral and skin temperature may persist following cessation of application of diathermy. In each observation of this series, the oral and skin temperatures were determined at fifteen-minute intervals for one hour after the current had been turned off. The results were as might be expected of partially nude subjects in an environmental temperature of 25.0 to 25.5° C. The oral temperature dropped to within normal limits in fifteen to thirty minutes. The skin temperatures decreased in similar fashion, but the feet of the normal subject usually were warmer at the end of the hour following cessation of application of short-wave diathermy than before the diathermy had been applied. In the presence of deficient arterial circulation, the decrease in temperature was of a

rapidity comparable to that of decrease of the temperature of normal subjects. However, because the maximal rise usually had been less than that observed in studies of normal subjects, the skin temperatures at the end of the hour closely approximated the previous temperatures at rest. These studies show that in our work the increased oral and skin temperatures are not maintained usually for longer than thirty minutes after cessation of application of diathermy. However, the increased oral and skin temperature induced by the diathermy may be maintained indefinitely by inhibiting the loss of heat through the skin. This may be done by covering the subject, with the exception of his head, with a cotton sheet and woolen blanket. We know from our experience with fever therapy that if a patient is surrounded by an insulating material, progressive hyperpyrexia will develop, and that the body temperature will be in direct relationship to the efficiency of the insulation and to the period over which the insulation is applied. It is thus easily possible to maintain the oral temperature of a patient at 99 to 100° F. for several hours or longer.

Application of short-wave diathermy in the clinical management of peripheral arterial occlusive disease seems indicated because of the favorable response thereto, as represented by the temperature of the skin. This study, however, was not to determine whether short wave diathermy was superior to other means of promoting vasodilation and, therefore, increased temperatures of the skin. We do feel that short-wave diathermy is an efficient means of inducing heat in the human body and, for this reason, its use should be considered in the care and study of patients with peripheral vascular disease.

It is to be remembered that the use of these high-frequency currents may be dangerous and that they should be applied only by persons trained in their application. If such care is observed, there is little, if any, danger. Because of the danger, however, we cannot advise their use in the home under the patient's control. Since overheating of any metal within the high-frequency field may occur, diathermy should not be applied over an inner-spring mattress. The current is most safely applied when the patient is lying on a wooden pallet covered by a hair mattress.

#### SUMMARY AND CONCLUSIONS

1. Short-wave diathermy applied to the trunk of the human body is a safe and efficient means of producing peripheral vasodilation of the lower extremities and, as such, should be of value in the management and study of peripheral vascular disease.

2. The use of the electromagnetic cable in a paneake formation under the lumbosacral region was found to be simpler in application and more comfortable in use than were several other possible applications of electrodes, and as efficient in operation as any of the other possible applications.

3. Short wave diathermy should be employed in the treatment of patients with peripheral vascular disease only under careful medical supervision.

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# CRYSTAL MICROPHONE FOR PULSE WAVE RECORDING

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TWO years ago a research on the deep systolic jugular pulse in tricuspid valve disease and in chronic "functional" tricuspid regurgitation by White and Cooke<sup>1</sup> occasioned the desire and demand for a simple method of simultaneously recording the electrocardiogram and pulsation in arteries or veins by means of paired galvanometers which would be more convenient than a galvanometer and the Frank capsule. There resulted a very satisfactory adaptation of the crystal microphone for pulse wave recording. Fig. 1 shows one of the simultaneous tracings of electrocardiogram and jugular pulse obtained at that time. It should be added that the connection may, of course, be made between the crystal microphone and a single galvanometer to obtain any solitary pulse tracing desired.

Various mechanical methods have been employed for many years to record the pulse wave. Some make use of lever systems in direct contact with the skin, so that the skin motion is magnified, and the tip of the final lever traces out the record on a moving surface. Other devices couple the lever system to the skin by an air column contained within a piece of rubber tubing. A pickup device (glycerine pelotte or a funnel) is applied to the skin and connected to one end of the tubing. The opposite end of the tubing is connected to a receiving tambour whose diaphragm actuates a recording lever system.

The vibration characteristics of these lever systems unfortunately are not suited to accurate recording of the pulse wave for two reasons. Their deflection speed is usually so slow as to obscure rapid fluctuations in the graph, and they are often not properly damped, so that they have a tendency to produce spurious vibrations in the record as a result of their own oscillation. In addition, slow deflection speed is accompanied by an apparent time lag in the recording of the pulse wave details. For example, the peak of the wave may appear on the tracing as if it occurred some time after the true peak pressure has been reached. When the natural frequency of vibration of the lever system is 5 cycles per second, an average figure for many mechanical recorders, this lag may be as much as 0.04 second. Such an error would be serious if an attempt were made to correlate the pulse wave with other cardiac events.

In an attempt to remove the distortion caused by slow deflection speed, an optical rather than a mechanical recording system was used and brought to a high state of perfection by Frank.<sup>2</sup> The air column

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coupling is retained, but the diaphragm at the far end of the tube carries a mirror which is arranged to twist as the diaphragm moves under the influence of the air pressure variations within the rubber tubing. A beam of light reflected from this mirror acts as an optical lever which is capable of providing a greatly magnified record of the mirror movement on a photographic film, without in any way adding to the inertia of the moving parts. This optical method can be made to have a deflection speed which is satisfactory for pulse recording. The damping is not easily controlled, but, if the deflection speed is great enough, no serious distortion will be introduced even if the device is not critically damped. The sensitivity of this apparatus is fixed by the particular diaphragm used and the distance from mirror to camera and is, therefore, not easily adjusted to suit varying conditions. The connection of the patient to the recording device by a length of rubber tubing introduces a time lag between the pulse and the motion of the recorder which depends upon the length of the tubing; this error in timing may be significant when the pulse is recorded simultaneously with some other cardiac event.

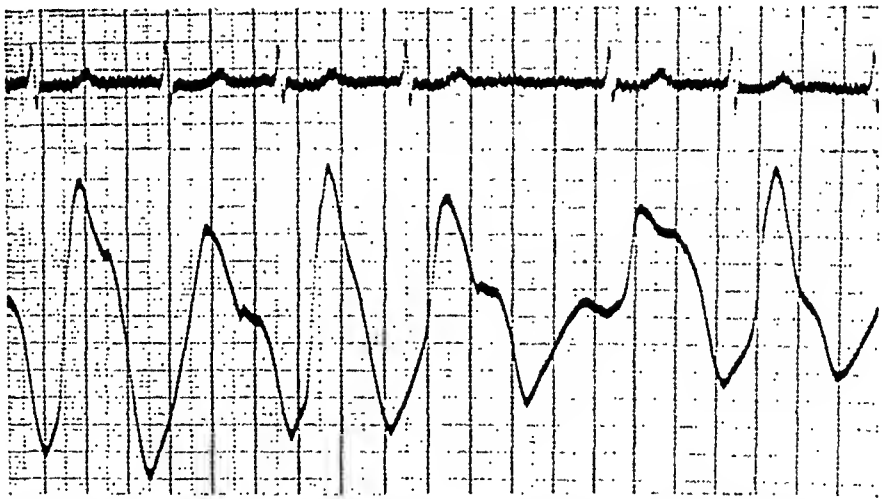


Fig. 1.—Simultaneous electrocardiogram (Lead I, above) and deep jugular pulse on the right side in a case of a woman, aged 49 years, with rheumatic heart disease, mitral stenosis, auricular fibrillation, and probable tricuspid valve disease. Note that frequently, especially during the longer diastolic periods, a stasis wave begins in the neck before systole, followed by the superimposition of the systolic jugular pulse 0.1 to 0.15 second after the upstroke of the R wave. The deep jugular pulse tracing was taken in the upright position with the receiver held over the sternocleidomastoid muscle and connected to a microphone, which was, in turn, attached to the string of one of the paired galvanometers. Time 0.1 second and 0.2 second. (This figure was published in the Transactions of the Association of American Physicians for 1939.)

The recording of the electrocardiogram is, of course, an electrical process. Heart sounds, although they have been recorded by the Frank method, are now almost universally recorded electrically. It would seem, therefore, that an electrical method of recording the pulse is desirable because of the greater ease of controlling the deflection speed, damping, and sensitivity, because of the possibility of eliminating long air columns, and finally, because of the simplification of technique which would result,

especially when the pulse tracing is recorded simultaneously with the electrocardiogram, the phonocardiogram, or both. The electrical method requires, first, changing the skin motion into electrical energy by some form of microphone. This may involve a short air column coupling from the skin to the diaphragm of the microphone. The output of the microphone, which will consist of a series of electrical impulses occurring at the cardiac rate, can then be recorded by a standard electrocardiograph amplifier and galvanometer system. The translation of the mechanical force (the pressure in the rubber tubing leading from the pickup device) into an electrical quantity may be accomplished by two fundamentally different methods. The first of these allows the mechanical force to control some variable element of an electrical circuit so that the current flowing in that circuit will vary in accordance with the applied force.

An example of this method is the ordinary carbon-grain telephone transmitter, which forms a variable resistance element in its associated circuit; this resistance is controlled by the force applied to the transmitter diaphragm. A sphygmograph using a carbon grain microphone and lever actuated by a solenoid was described by Waud<sup>3</sup> in 1924, and in 1928, Turner<sup>4</sup> introduced a sphygmograph made up of a carbon grain microphone and string galvanometer. The carbon microphone has not been satisfactory for measurement or recording work because of its instability and its generation of internal noise. Other possibilities in this control method are the uses of condenser<sup>5</sup> or inductance elements as the microphone. Although these devices are stable and noiseless, the relative complexity of the circuits with which they must be associated has hindered their general adoption for clinical applications.

The second method of changing mechanical into electrical quantities is the generation method, whereby the mechanical energy actuates some form of electrical generator which converts the mechanical energy directly into electrical energy. One form of generator which appears to be peculiarly adapted to the particular problem of pulse recording is the crystal microphone. This device is based upon the property which some crystals have of generating an electrical voltage when the crystal itself is twisted or squeezed; the magnitude of the voltage is proportional to the applied force. The electrical energy is led off from the crystal by thin, metal-foil electrodes, cemented to opposite faces of the crystal. The combination of the electrodes and crystal, when no pressure is applied to the crystal, forms a condenser of definite capacity. When pressure is applied to the crystal, the condenser appears to have had a generator added to it. Electrically, therefore, the crystal microphone may be represented by a generator in series with a condenser, as shown in Fig. 2. The electrical energy developed within the crystal is too small to be used directly with recording instruments. It is necessary, therefore, to insert an amplifier between the microphone and

recording instrument. The load which the amplifier presents to the microphone will be essentially a resistance (the grid leak of the first tube). The voltage delivered to the amplifier ( $E_a$ ) will differ from that developed by the microphone ( $E_i$ ) because of the presence of the condenser ( $C$ ). The distortion introduced by the capacity  $C$  is a function of the rate at which the voltage  $E_i$  is varying and the relative sizes of  $C$  and  $R$  (resistance). The relative sizes of  $C$  and  $R$  can be gauged by a single factor, namely, their product  $RC$ , known as the "time constant"

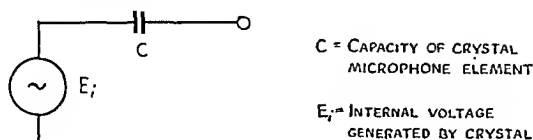


FIG. 2

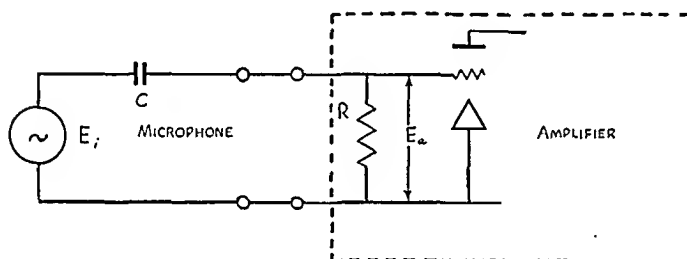


FIG. 3

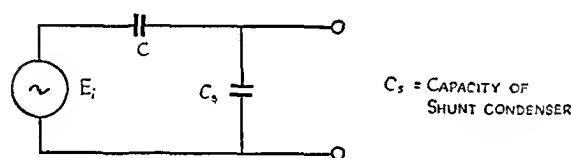


FIG. 4

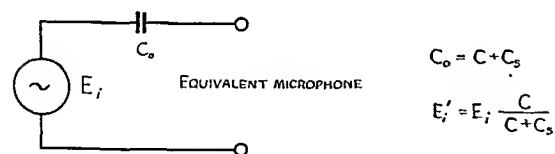


FIG. 5

Figs. 2-5.

of the  $RC$  circuit. If  $C$  is measured in microfarads and  $R$  is given in megohms (1 megohm equals 1,000,000 ohms), this product gives the time constant directly in seconds.

In order that the voltage delivered to the amplifier shall be a reasonably accurate copy of the voltage generated by the microphone, and,

if we bear in mind that the generated voltage is varying at the rate of the heartbeat, it is necessary that the time constant be of the order of several seconds. This question of the relation of the time constant of recording circuits to the rate of variation of the voltage to be recorded has been discussed in a quantitative manner in a paper by Schwarzschild and Kissin.<sup>6</sup>

The capacity of the crystal elements used in microphones is of the order of only several thousandths of a microfarad. The value of  $R$ , therefore, would have to be about 1,000 megohms in order to satisfy the requirement that the product  $RC$  shall be several seconds. The use of an amplifier input resistance of such an enormously high value is not practical, however, because of the unavoidable shunting effect of leakages through the crystal, the wiring, and the grid current taken by the first amplifier tube. It is this practical limitation which renders the crystal microphone in its usual form unsuitable for pulse wave recording.

In order that the amplifier input resistance be kept at a reasonable value (several megohms), the microphone capacity would have to be of the order of 1 microfarad. The capacity of the crystal microphone may be artificially increased by the simple expedient of shunting an external fixed condenser across it, as shown in Fig. 4. If the circuit of Fig. 4 is analyzed, it will be found to be exactly equivalent to a new microphone whose capacity is represented by  $C_0$  and whose internal voltage is  $E_1'$ . It is seen that the microphone may be given any desired capacity, but that the available voltage is reduced in the same ratio as the capacity is increased. The choice of the shunt capacity becomes a compromise between large capacity and more accurate recording on the one hand, and small capacity and higher output on the other hand.

Fortunately, the pressure variations obtainable from the pulse are so great in comparison with the sound pressure variations for which the microphone is designed, and the inherent crystal microphone sensitivity is so high that, even after reducing the sensitivity and raising the capacity several hundred times by the use of a 1-microfarad shunt condenser, the available output voltage is still in the neighborhood of 1 millivolt. A millivolt impulse is of the correct magnitude to be easily recorded by a standard amplifier type of electrocardiograph. When a standard amplifier type of electrocardiograph is available, and, if its input resistance is several megohms, a crystal microphone may be adapted for pulse wave recording by shunting a 1-microfarad condenser across it and connecting the combination directly to the electrocardiograph input.

When it is desired to use a string galvanometer as the recording instrument, it will be necessary to design a suitable amplifier to couple the crystal to the string, because the low resistance of the string precludes its use directly.

The microphone itself should be mounted in an airtight housing, so that the air column of the pickup device (funnel or pelotte), the rubber tubing, and the microphone diaphragm form a completely sealed space. The skin motion is then converted into pressure variations within this enclosed volume of air which actuate the microphone diaphragm.

Since the wires from the microphone to the recording equipment may be any length and the microphone is small and requires no elaborate supporting fixtures, the rubber tubing between microphone and pickup need be only a few inches in length. This avoids the time lag introduced by the transmission of air pressure variations through long tubes.

The deflection speed and damping of a properly adjusted electrocardiograph are such as to insure accurate recording of the pulse, which is relatively less complicated and contains more slowly varying waves than the electrocardiogram itself. Continuous control of the sensitivity over a wide range, which is not practical with the mechanical systems or with the Frank capsule, is, of course, easily accomplished with the sensitivity control with which the electrocardiograph is already equipped. The possible distortion introduced by the coupling condenser effect of the microphone itself, or by the condensers within the amplifier, does not change the timing of the events in the pulse cycle, and therefore it does not impair the diagnostic value of the resulting curves. It is simply an addition to the possible distortion already unavoidably introduced into the recording system by the interposition of the wall of the blood vessel and its surrounding tissues.

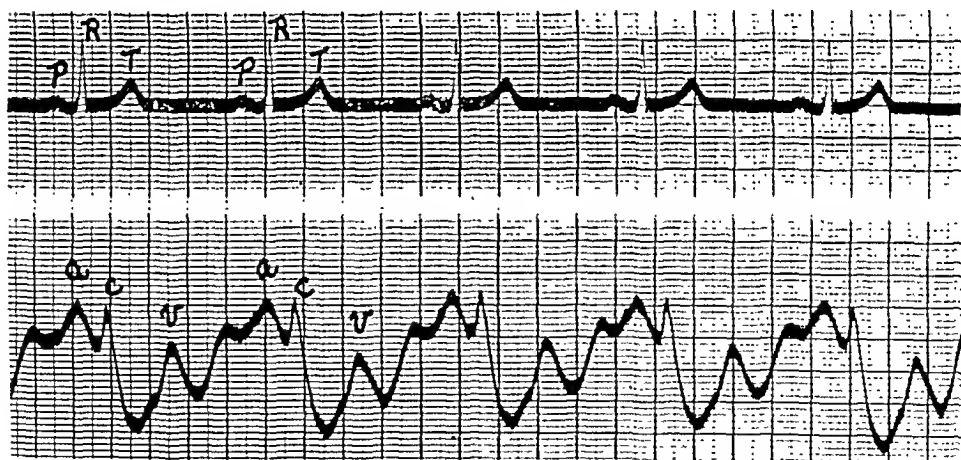


Fig. 6.—Simultaneous Lead II of the electrocardiogram, above, and jugular pulse tracing by the use of the crystal microphone and string galvanometer, below, in the case of a healthy young man.

A photograph of the crystal microphone (piezoelectric) sphygmographic attachment for use with the galvanometer was published by Rappaport and Sprague in their paper entitled "Physiologic and Physical Laws That Govern Auscultation, and Their Clinical Application."\*

\*AM. HEART J. 21: 257, 1941; see Fig. 21.

Fig. 6 is an example of a normal jugular pulse tracing taken by the use of the crystal microphone simultaneously with Lead II of the electrocardiogram.

#### SUMMARY AND CONCLUSIONS

Pulse wave recordings obtained indirectly by instruments coupled to the skin may be affected by the blood vessel wall and surrounding tissues, but this effect is not of great clinical significance, whereas the important requirements of correct timing of pulse wave details and freedom from spurious waves cannot be met by purely mechanical recorders and are met with difficulty by optical devices. Neither of these types of recorders is especially convenient, particularly when simultaneous tracings of the pulse and other cardiac events are taken.

These difficulties may be overcome by electrical recording methods. Specifically, we have shown how a crystal microphone may be adapted to give satisfactory pulse tracings by using an electrocardiograph amplifier and galvanometer as the recording system.

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# THE CIRCULATORY ADJUSTMENTS IN POLYCYTHEMIA VERA

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FEW observations of the cardiac output and related functions of the circulation have been made on patients suffering from polycythemia vera. The earlier observations of Bergmann and Plesch,<sup>1</sup> Loewy,<sup>2</sup> Mohr,<sup>3</sup> and Röver<sup>4</sup> revealed no significant variation in cardiac output from normal. Liljestrand and Stenström,<sup>5</sup> using the method of Krogh and Lindhardt, found a decrease of 10 per cent in the cardiac index, while Ernst<sup>6</sup> found an increase of 10 per cent. More recently Goldsmith<sup>7</sup> has made observations employing the acetylene method of Grollman. In one patient, observed for eight months, the cardiac output was elevated when the amount of hemoglobin and the count of the red blood cells were higher than normal, and decreased as these fell toward normal. From an analysis of the case history of this patient, together with the observation of the persistently elevated basal metabolic rate, it is not clear that the changes in the circulation represent the effect of polycythemia vera alone. In two other patients observed by Goldsmith, the values were within normal limits, and in the fourth, the cardiac output was slightly increased. Thus, neither Goldsmith's nor other data in the available literature allow a final conclusion as to what changes occur in the circulation of patients suffering from polycythemia vera.

In an attempt to clarify the present state of our information, we have made studies of the cardiac output, oxygen consumption, cardiac size, left ventricular work, and other related functions of the circulation in six patients suffering from polycythemia vera.

## METHODS

All observations were made in the morning while the patients were in a basal metabolic state. Measurements of the cardiac output were made by the acetylene method, three samples of gas being taken as first recommended by Grollman,<sup>8</sup> and as further elaborated by Grollman, Friedman, Clark, and Harrison.<sup>9</sup> The Grollman technique can be applied to these patients since the oxygen saturation of the arterial blood in polycythemia vera, when the patient is at rest, is normal, or only slightly less than normal<sup>10, 11</sup> (Cases 1 and 7, Table II); more-

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over, the solubility of acetylene in polycythemic blood is so slightly less than in normal blood that it makes no appreciable difference in the final calculations (Grollman<sup>12</sup>). During rebreathing, the patients were sitting in a steamer chair (angle 135°) with legs extended. They were acquainted with and trained to carry out the procedures beforehand. While the patient was at rest, the cardiac rate was counted at intervals of five minutes. At the end of one hour the acetylene-air-oxygen mixture was rebreathed. Three samples of gas were taken during each rebreathing period for estimation of the arteriovenous oxygen difference. The first sample was taken after rebreathing 10 to 12 times in 20 seconds, the second after 2 to 3 breaths more, and the third after 2 to 3 additional breaths. All three samples were usually obtained before the end of 30 seconds. Samples were taken during expiration. Two periods of rebreathing were carried out on each patient. Shortly afterwards, the oxygen consumption was measured with a Benedict-Roth spirometer. After a short pause, the vital capacity was measured and height and weight were ascertained. In succession, sufficient time being allowed between each procedure for the patient to return to a basal metabolic state, the three standard leads of the electrocardiogram and a chest lead were taken, the arm-to-tongue circulation time recorded, the venous pressure estimated, the blood pressure measured, and a roentgenogram of the heart made at a distance of two meters.

The arm-to-tongue circulation time was estimated by the use of decholin.<sup>13</sup> Five c.c. of a 20 per cent solution were injected rapidly (1 to 2 seconds) through an 18 gauge needle into an antecubital vein while the patient was lying quietly in the supine position. This was repeated one and one-half minutes after the response to the first test had been elicited. The time was recorded from the beginning of the injection until the patient perceived the bitter taste.

The venous pressure was measured by the direct method,<sup>14</sup> using a large antecubital vein, the arm being placed on a level with the right auricle. The system was filled with normal saline and the venous pressure read directly from a scale as millimeters of saline. Normal pressures by this method range from 40 to 100 mm. of saline.<sup>15</sup> In subsequent measurements the vein was entered at the site first punctured, the vein of one arm being reserved for measurement of venous pressure, and of the other arm for estimation of the circulation time.

Roentgenograms of the heart were taken with the patient in the standing position, in full inspiration, at a distance of two meters. Measurements of the cardiac area were carried out by the technique of Levy.<sup>16</sup>

In two patients (Cases 1 and 7), estimations of the oxygen content of the blood were made. Samples of arterial blood were taken under

albolene from a radial or brachial artery, and of venous blood, without stasis, from an antecubital vein, the same vein being used for this purpose each time. The oxygen content of these samples was estimated by the Van Slyke and Neill manometric method.<sup>17</sup> Samples of blood were taken in the morning before breakfast with the patient in a basal metabolic state.

The effect of the polycythemic state on the work of the left ventricle per beat was calculated by making use of the formula<sup>18</sup>  $W = QR + \frac{wV^2}{2g}$ , in which  $W$  equals work done per beat;  $Q$  equals volume of blood expelled per beat;  $R$  equals mean arterial blood pressure in mm. of Hg  $\times 13.6$ ;  $V$  equals velocity of blood at aorta;  $w$  equals weight of blood; and  $g$  equals acceleration due to gravity. The last part of the formula,  $\frac{(wV^2)}{2g}$ , has been omitted (Starr<sup>19</sup>). By substituting values in the formula, the work of the left ventricle per beat has been calculated. Since there is evidence<sup>20</sup> that the work of the right ventricle bears a constant relationship to that of the left, we have concerned ourselves only with the latter.

#### OBSERVATIONS

Observations were made on 6 patients suffering from polycythemia vera who exhibited a wide range in the amount of hemoglobin and in count of the red blood cells. In one patient (Case 1), it was possible to make observations not only during the polycythemic state, but also later when anemia had occurred as a consequence of therapy, and again when normal levels of the red blood count and hemoglobin were restored. None of the patients exhibited signs or symptoms of congestive heart failure at the time when observations were made. Examination of the heart revealed no abnormalities except in the case of F. M. (Case 1) who exhibited slight enlargement of the heart.

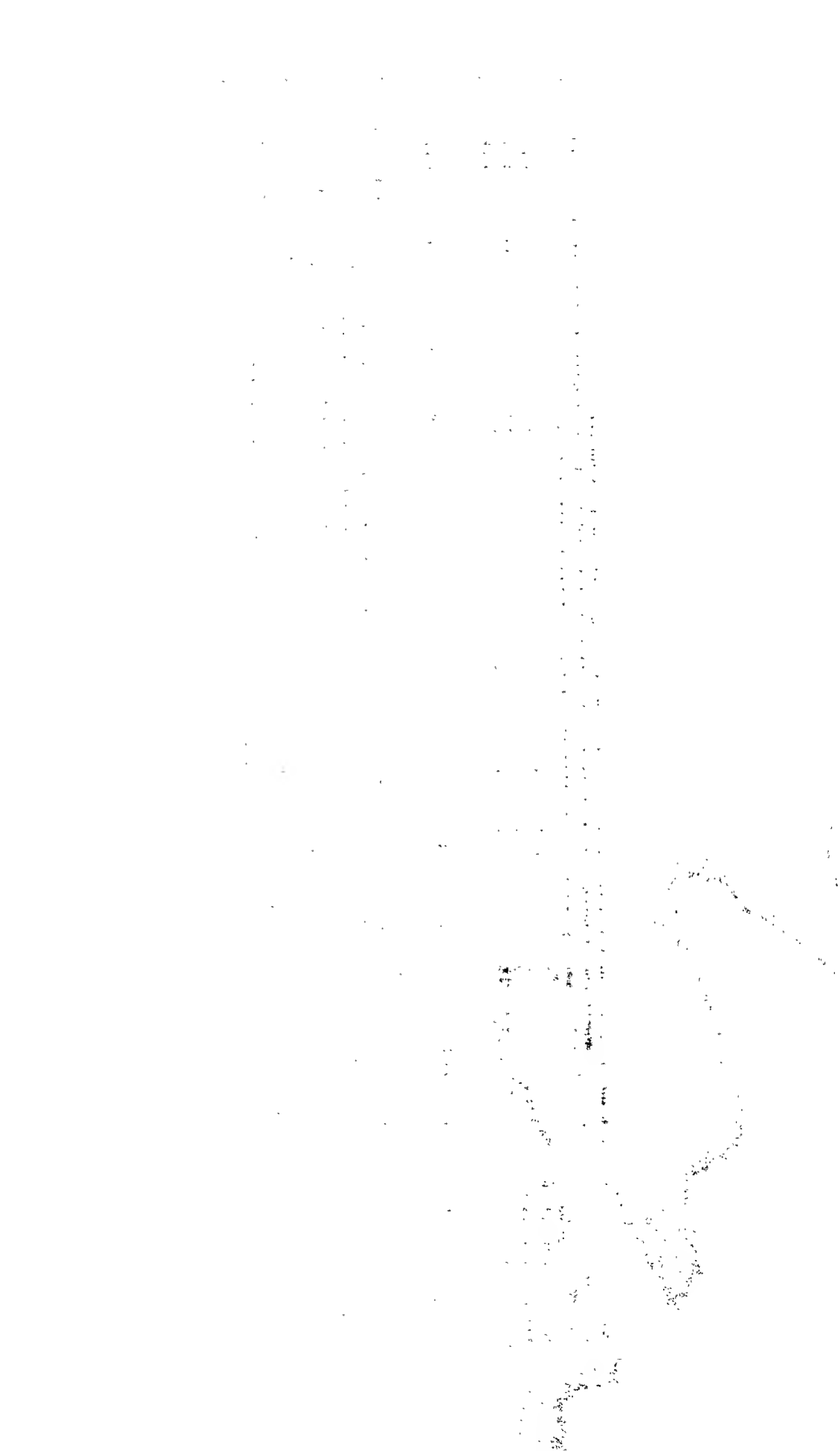
CASE 1.—F. M., History No. 62980, male, aged 34 years, was admitted to hospital on April 30, 1934. He had observed blueness of the hands and feet for three years, and during this period had suffered from drowsiness and frontal headaches. Examination revealed purplish red cyanosis of the skin and mucous membranes, many small, fresh hemorrhages in both optic fundi, enlargement of the spleen, and edema of the ankles. The count of the red blood cells was 9.4 million and the hemoglobin amounted to 158 per cent. The electrocardiogram showed normal sinus rhythm; right axis deviation was present. A roentgenogram of the heart showed enlargement both to the right and to the left. Treatment with acetylphenylhydrazine, x-radiation, and venesection was instituted. Studies of the circulation were made on May 26, 1934, at a time when the amount of hemoglobin and the count of the red blood cells were far above normal (Table I, Fig. 1), on June 16, 1934, when they were far below normal, as a result of intensive treatment, again on July 27, 1934, during recovery from anemia, and finally on October 11, 1934, and January 9, 1935, when they had attained normal values. Observations relating to the blood gases were made on October 13, 1934 (Table II).

TABLE I  
MEASUREMENTS OF THE CIRCULATION IN SIX PATIENTS SUFFERING FROM POLYCYTHEMIA VERA

AGE, YR.	SEX	DATE	HEIGHT, CM.	WEIGHT, KG.	BODY SURFACE AREA, SQ.M.	OXYGEN CONSUMPTION, C.C. PER MIN.	BASAL METABOLIC RATE, PER CENT	ARTERIOVENOUS OXYGEN DIFFERENCE, C.C.	CARDIAC OUTPUT, L./MIN.	CARDIAC OUTPUT, L./SQ.M./MIN.	HEART RATE, PER MIN.	STROKE VOLUME, C.C. PER BEAT	CARDIAC AREA, SQ.CM.	CARDIAC VOLUME, C.C.	ARTERIAL PRESSURE, MM. HG	LEFT VENTRICULAR WORK, GM. M./BEAT	CIRCULATION TIME, SEC.	VENOUS PRESSURE, MM. SALINE	VITAL CAPACITY, C.C.	RED BLOOD COUNT, MILLIONS	HEMOGLOBIN, * PER CENT	CARDIO-THORACIC RATIO, PER CENT
Case 1, F. M.	M	5/26/34	176.8	86.9	2.04	286	+2	75.5	3.79	1.86	98	39	175.8	1126.3	110/	85/52.0			3300	7.4	128	52.1
		6/16/34	178.0	84.4	2.03	272	-2	57.0	4.77	2.35	92	52	162.7	1001.2	110/	75/65.8			3850	3.6	60	50.1
		7/27/34	177.5	87.4	2.06	276	-2	65.1	4.24	2.06	78	54	162.7	1001.2	120/	76/72.0	14.8		3750	3.7	94	48.1
		10/11/34	179.0	93.0	2.12	280	-3	62.2	4.50	2.12	80	56	160.2	980.5	142/	86/86.8	17.7	45	3900	5.5	110	50.7
		1/ 9/35	176.5	90.6	2.09	282	-2	63.1	4.47	2.14	86	52	163.2	1007.0	130/	90/77.8				4.8	94	
Case 2, H. A.	F	1/ 8/38	157.5	71.5	1.72	288	+43	96.5	3.00	1.74	92	33	142.2	819.4	165/100	59.7	14.1	54	2050	8.3	160	50.1
Case 3, A. G.	M	10/24/34	175.0	77.5	1.93	228	-9	63.4	3.60	1.86	76	47	149.2	880.9	150/	90/76.7	21.5		4800	7.1	108	45.9
Case 4, L. L.	M	1/13/36	162.5	54.3	1.58	209	+2	67.5	3.09	1.96	72	43	122.4	655.1	110/	80/55.6	17.7	58	3300	6.8	150	44.3
Case 5, I. S.	M	11/13/34	162.8	58.2	1.61	220	+4	61.9	3.55	2.20	63	56	137.8	781.8	160/	90/95.2	12.2		3650	4.7	94	46.8
Case 6, E. D.	F	1/ 8/40	161.0	68.3	1.72	224	+8	77.9	2.87	1.67	74	39	105.2	522.1	124/	80/54.1	15.8	69	2400	7.5	138	50.9

\*14.5 grams equivalent to 100 per cent

\*14.5 grams equivalent to 100 per cent.



CASE 2.—H. A., History No. 191222, white female, aged 50 years, was admitted to hospital on January 6, 1938. She had suffered from dizziness and flashes of light before the eyes for five years. During this time her complexion had become progressively more florid. Examination showed deep reddish cyanosis of the skin and mucous membranes, distention of the veins of the retinae, generalized venous engorgement, enlargement of the liver to three fingerbreadths below the right costal margin, and of the spleen to two fingerbreadths below the left costal margin. In the electrocardiogram normal sinus rhythm and left axis deviation were present. A roentgenogram of the heart revealed no deviation from the normal. Studies of the circulation were made on January 8, 1938, at a time when the hemoglobin amounted to 160 per cent and the count of the red blood cells was 8.3 million (Table I, Fig. 1).

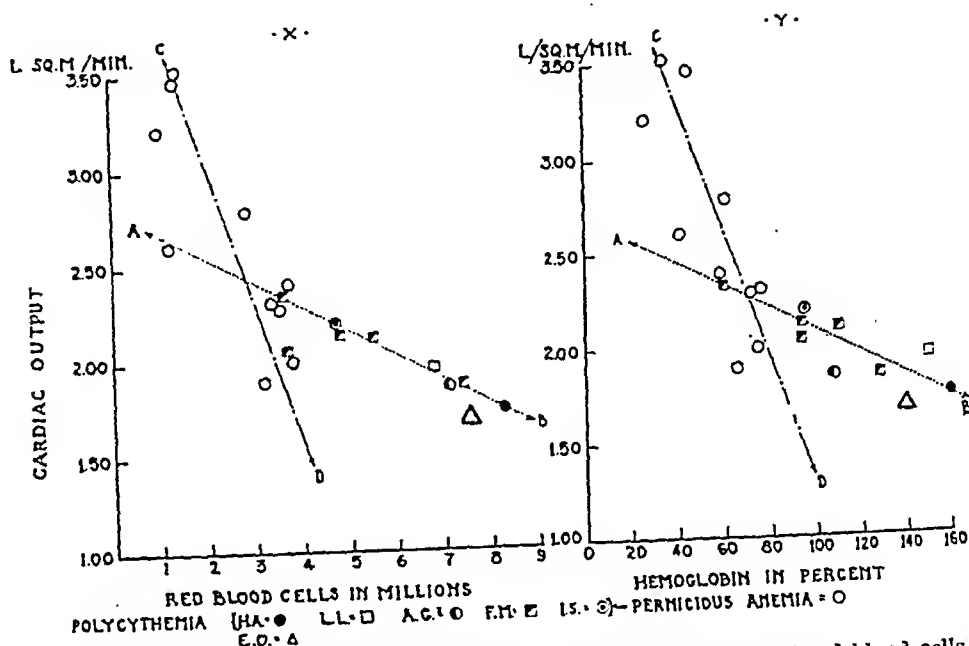


Fig. 1.—Cardiac index, red blood cells and hemoglobin. Counts of red blood cells of patients suffering from polycythemia vera and pernicious anemia are plotted against the corresponding cardiac indices in Fig. 1X, while estimations of hemoglobin of the same patients are plotted against corresponding cardiac indices in Fig. 1Y. In each instance, there is a linear correlation, in that as the red blood cell count and the amount of hemoglobin increase, the cardiac output decreases. Furthermore, in each instance, the slant of the line for polycythemia vera (line AB) is different from that for pernicious anemia (line CD). Each symbol represents a patient; a different symbol is used for each patient suffering from polycythemia vera, but the same symbol (open circle) is used for all the patients suffering from pernicious anemia (21).

CASE 3.—A. G., History No. 20387, male, aged 46 years, was seen in the Out Patient Clinic on October 24, 1934. He had suffered from intermittent claudication for three years. Examination revealed cyanosis of the lips and the nail beds, florid skin, enlargement of the liver to one fingerbreadth below the right costal margin, and of the spleen to four fingerbreadths below the left costal margin. Electrocardiogram showed right intraventricular heart block and normal sinus rhythm. A roentgenogram of the heart showed no deviation from the normal. Studies of the circulation were made on October 14, 1934, at a time when the hemoglobin amounted to 108 per cent and the count of the red blood cells 7.1 million (Table I, Fig. 1).

CASE 4.—L. L., History No. 48688, male, aged 47 years, was admitted to hospital on December 22, 1936. He had suffered from symptoms of diabetes mellitus for 3 years. Examination revealed dusky cyanosis of the lips, nail beds, and skin, distention of the veins of the retinae, and enlargement of the spleen to two finger-

breadths below the left costal margin. The electrocardiogram was essentially normal. A roentgenogram of the heart showed no deviation from the normal. Studies of the circulation were made on January 13, 1937, at a time when the hemoglobin amounted to 150 per cent and the count of the red blood cells was 6.8 million (Table I, Fig. 1). At the time these studies were made, the diabetes mellitus was controlled by dietetic management and the use of insulin.

CASE 5.—I. S., History No. 55412, male, aged 43 years, was admitted to the Out Patient Clinic in August, 1934. He had suffered from intermittent claudication, dyspnea, substernal oppression on exertion, and attacks of throbbing headache for one year. Examination revealed reddish cyanosis of the mucous membranes, and enlargement of the spleen to the left costal margin. The hemoglobin amounted to 144 per cent and the count of the red blood cells was 6.8 million. Treatment with acetylphenylhydrazine was instituted. On November 13, 1934, the hemoglobin had fallen to 94 per cent and the count of the red blood cells to 4.7 million. On this date, slight cyanosis was still present; the spleen could no longer be palpated. An electrocardiogram showed normal sinus rhythm, and slight changes in the form of the T waves and R-T segments which were thought to be suggestive of coronary artery disease. A roentgenogram of the heart showed no deviation from the normal. Special studies of the circulation were made on November 13, 1934 (Table I, Fig. 1).

CASE 6.—E. D., History No. 28897, white female, aged 47 years, was admitted to hospital on January 2, 1940. She had suffered from headaches, sensation of fullness in the head, and fleeting pain, numbness and tingling in the extremities, for seven years. Examination revealed a plethoric individual, with bluish cyanosis of the lips and nail beds, enlargement of the liver to just below the right costal margin and of the spleen to 7 cm. below the left costal margin. Normal sinus rhythm and left axis deviation were present in the electrocardiogram. In the roentgenogram of the heart, there was no deviation from normal. Special studies of the circulation were made on January 8, 1940, at a time when the hemoglobin amounted to 138 per cent, the count of the red blood cells was 7.5 million and the red blood cell volume was 58 per cent.

In summary, it appears from the data of Table I (Fig. 1) that, when the quantity of hemoglobin and the count of the red blood cells were increased above normal, the arteriovenous oxygen difference was increased and the cardiac output per beat and the cardiac index were decreased. Measurements of the oxygen consumption, heart rate, blood pressure, venous pressure, and the vital capacity showed no consistent variation from the normal. The data concerning the circulation time were insufficient for analysis.

#### DISCUSSION

These data demonstrate that the increase in red blood cells and in hemoglobin in polycythemia vera is associated with a decrease in volume output of the heart. Furthermore, it appears that increase in the arteriovenous oxygen difference and decrease in the cardiac output is proportional to increase in the amount of hemoglobin and augmented number of the red blood cells, and that these relationships are linear (Fig. 1). For, with the decrease in hemoglobin and in

the count of the red blood cells under therapy, the arteriovenous oxygen difference decreased to normal and the cardiac output increased. When anemia occurred (Case 1), the arteriovenous oxygen difference decreased further still and the cardiac output increased beyond normal, just as we have observed in patients suffering from pernicious anemia<sup>21</sup> (Fig. 1). There appears to be a difference between pernicious anemia and polycythemia vera, however, with respect to the relationships existing between the values for hemoglobin and red blood cells on the one hand, and arteriovenous oxygen difference and cardiac output on the other. When the data from Stewart, Crane, and Deitrick's paper relating to patients suffering from pernicious anemia<sup>21</sup> are plotted on the same chart with those of our six patients suffering from polycythemia vera (Fig. 1), the lines are not continuous as we ascend the scale of values for hemoglobin and red blood cells. The slant of the line for pernicious anemia (Fig. 1, line *CD*) is steeper than that for polycythemia vera (Fig. 1, line *AB*). The increased basal metabolic rate<sup>21</sup> in pernicious anemia no doubt accounts for part of the divergence in the slope of these lines.

In five of these patients (Cases 2, 3, 4, 5, and 6), calculation of the cardiothoracic ratios did not reveal significant change in the size of the heart. In the other patient (Case 1), the cardiothoracic ratio was slightly increased. With respect to the size of the heart, it is of interest to analyze the heart size in relationship to the work of the heart. When the cardiac volumes were plotted as abscissae and the gram-meters of work of the left ventricle as ordinates, in accordance with the method of Starr and his co-workers,<sup>19, 22</sup> we noted that all our observations except one fell within the zone of normal circulatory function, indicating that the work of the heart was commensurate with its size.

Since none of our patients exhibited symptoms or signs of heart failure, and since rise in venous pressure was not recorded either in our patients or in those reported by Gibson, Harris, and Swigert,<sup>23</sup> and since the work of the heart in our patients was commensurate to its size, it appears to us that the increase in the arteriovenous oxygen difference and the decrease in cardiac output per beat and cardiac index which we have observed results not directly from impairment of cardiac function in polycythemia vera, but rather as a consequence of, and in order to compensate for, the abnormalities resulting from increase in the amount of hemoglobin and the count of the red blood cells.

In polycythemia vera the blood volume,<sup>23, 24</sup> and viscosity<sup>24, 25</sup> are increased, the velocity of blood flow is decreased,<sup>23</sup> and the capillaries throughout the body exhibit engorgement and retardation of the

blood flow through them,<sup>26, 27</sup> and from these data now being presented, the minute volume output of blood is decreased. The slowing and stagnation of the circulating blood results in lowering of the oxygen content of the venous blood, and provides an explanation of the increased arteriovenous oxygen difference which we observed in our patients, in whom neither symptoms nor signs of heart failure nor increases in the basal metabolic rate were observed. This notion is further borne out by the increase in percentage oxygen utilization observed in one of our patients (Case 6, Table II). Furthermore, in polycythemia vera there is marked increase in the oxygen content of the arterial blood<sup>10, 11</sup> (Case 7,<sup>6</sup> Table II). Since each unit volume of polycythemic blood contains an unusually large quantity of hemoglobin, the oxygen requirement of the tissues can be satisfied by a cardiac output which is smaller than normal, and the maintenance of a normal cardiac output under these circumstances would impose needless work on the heart. It appears likely, therefore, that the decrease in cardiac output which we observed in our patients represents adaptation of the circulatory mechanism to avoid needless work. This notion is supported by the observations of Grollman,<sup>8</sup> that when an individual moves from sea level to dwell at a high altitude, the cardiac output first increases, but then decreases as polycythemia develops, allowing increased oxygen carrying capacity of the blood to replace increased cardiac output as a means of supplying the tissues with their oxygen requirement.

#### SUMMARY

1. Measurements of cardiac output by the acetylene method, and of related circulatory functions, have been made on six patients suffering from polycythemia vera, and studies of the blood gases have been made on one of these patients, as well as on another subject suffering from polycythemia vera.

2. At a time when the amount of hemoglobin and the count of the red blood cells were increased above normal, the arteriovenous oxygen difference was increased, the cardiac output per beat and the cardiac index were decreased, and the oxygen content of both the arterial and venous blood was increased. Left ventricular work, cardiac size, basal metabolic rate, blood pressure, and other functions of the circulation studied showed no consistent variation from normal. When reduction of the level of hemoglobin and red blood cells occurred as a result of therapy, the arteriovenous oxygen difference decreased and the cardiac index and output per beat increased and attained normal

\*This patient was a white male, aged 42 years, who was observed in the Hospital of the Rockefeller Institute for Medical Research over a period of five months in 1926. He had suffered from symptoms of polycythemia vera for five years and on examination revealed findings typical of this disease, but no other abnormalities. The blood pressure measured 130/100 mm. Hg, and the basal metabolic rate +18.7 per cent. We wish to thank Dr. Alfred E. Cohn of the Hospital of the Rockefeller Institute for Medical Research for permission to use these data.



values when the red blood cells and hemoglobin reached normal levels. There was a linear relationship between quantity of hemoglobin and number of red blood cells on the one hand, and the cardiac output and the cardiac index on the other. These changes in circulation may be compensatory mechanisms which spare the heart part of the burden of pumping an increased total volume of circulating blood having an increased viscosity at a normal velocity.

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## Department of Clinical Reports

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### AN UNUSUAL CASE OF CONGENITAL HEART DISEASE IN A WOMAN WHO LIVED FOR FORTY-FOUR YEARS AND SIX MONTHS

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THE interest of the medical profession in the diagnosis of congenital anomalies has been stimulated in recent years by comprehensive pathologic, physiologic, and clinical observations. Maude Abbott's<sup>1</sup> work in this field has been outstanding, and she has suggested a practical classification. It is briefly as follows:

1. Cyanotic group (no abnormal communication). Examples: coarctation of aorta, bicuspid aortic valve.
2. Cyanose tardive (arterial-venous shunt with temporary or terminal reversal of flow). Examples: Patent ductus arteriosus, patent foramen ovale, interventricular septal defect.
3. Cyanotic group (permanent venous-arterial shunt). Examples: tetralogy of Fallot, Eisenmenger complex.

The vast majority of congenitally diseased hearts are seen by pediatricians, as the more severe and complex lesions are usually fatal in early life. However, lesions falling into the cyanotic group are frequently overlooked or minimized in this period, and likewise, anomalies resulting in arterial-venous shunt are often asymptomatic and may also be overlooked until the stress and strain of advancing years have been added. Consequently, cases in these two groups are those most commonly seen in adults. Rarely do the patients with permanent venous-arterial shunt reach the third decade or beyond. However, our patient, who died in her forty-fifth year, belonged to this third group.

Of the various congenital cardiac anomalies resulting in permanent cyanosis, the tetralogy of Fallot (consisting of pulmonic stenosis, right ventricular hypertrophy, patent interventricular septum, and dextro-position of the aorta) is the most common. The average length of life of eighty-three such patients studied by Maude Abbott<sup>1</sup> was 12.75 years. It was not until 1929 that the maximum life span of 59 years and 9 months was reported by White and Sprague.<sup>2</sup> The mean age of thirty patients with pulmonic atresia with interventricular septal defect and dextro-position of the aorta was 5 years, with a maximum age of 30 years.<sup>3</sup> Seventeen patients with transposition of the arterial trunks with

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interventricular septal defect had a mean age of 2.75 and a maximum age of 16 years.<sup>3</sup> The short duration of life in these cases is noteworthy, and consequently, when a similar group of anomalies is found to exist in an adult, it is of considerable interest.

Our patient, a single, white female, 35 years of age, was first admitted to the Wisconsin General Hospital in November, 1926. Her chief complaint was pain in the upper abdomen. For several years she had experienced intermittent sharp upper abdominal pain associated with nausea. This was not related to food, exercise, or time of day. She had always been dyspneic and cyanotic, and had been told that she had a cardiac murmur from early childhood. Consequently, she had led a rather quiet life, but in general, had been comfortable.

On physical examination there was cyanosis of the lips and nail beds and marked clubbing of the fingers and toes. The chest was somewhat deformed, with a prominent angle of Louis. The heart was enlarged to both right and left. (No definite measurements were recorded.) There was a rough systolic murmur maximum over the pulmonic area; it was widely transmitted over the precordium, but chiefly upward into the left carotid. The second sound at the base was reduplicated. The blood pressure was 150/70; the cardiac rate, 54 to 56; and the rhythm, regular. Hemoglobin was 93 per cent (Tallqvist method), and the erythrocyte count was 5,688,000. An electrocardiogram showed complete heart block (auricular rate 85, and ventricular rate 42), with marked right ventricular preponderance.

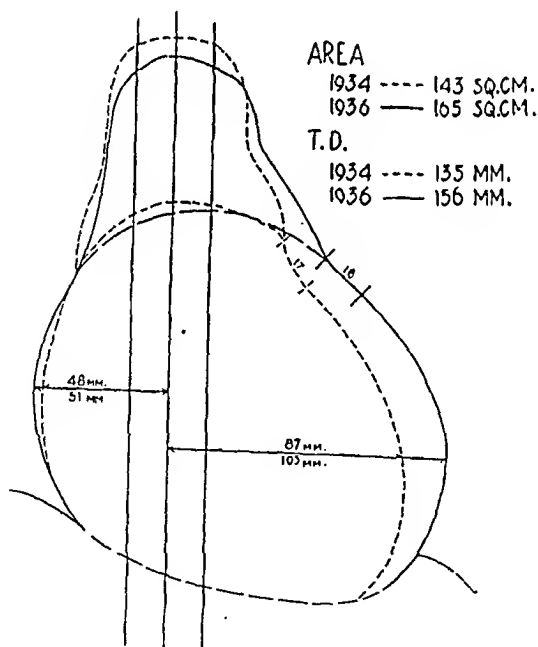


Fig. 1.

She returned on Nov. 13, 1928. The only significant variation in symptoms was an increase in the amount of dyspnea. The degree of cardiac enlargement was believed to be slightly increased. A right ovarian cyst, about 7 cm. in diameter, was now present. Otherwise, the physical findings were essentially unchanged.

Upon examination on Dec. 13, 1934, an orthodiagram was first made. This showed a prominent pulmonic arch, a normal left auricular salient, a narrow retrocardiac space, and marked cardiac enlargement, with a +68 per cent deviation in frontal area and a +21 per cent deviation in transverse diameter. The maximum left diameter was 87 mm., and the right, 48 mm. (Fig. 1).

Her final admission was Sept. 21, 1936. She had continued to be quite active, doing all of the housework for aged parents and herself. On examination it was noted that mentation was sluggish. Dyspnea at rest was present for the first time. Cyanosis had increased. Examination of the circulatory system showed a regular pulse, with a rate of 45. Blood pressure was 125/90 in the right arm and 135/90 in the right leg. The apex impulse was visible and palpable in the fifth interspace 10.5 cm to the left of the midsternal line. There was moderate apical and precordial heaving. The pulmonic second sound was widely split and greater than the aortic second sound. A moderately loud, harsh, systolic murmur was maximum at the pulmonic area, and distinctly heard over the suprasternal notch and in the carotid vessels. A somewhat softer systolic murmur was audible over the sternum at the level of the third and fourth ribs, transmitted to the apex and left axilla. A soft, blowing, early diastolic murmur was best heard along the left sternal border, but was not audible at the aortic area. The liver was palpable 3 cm. below the right costal margin at the midclavicular line. The lungs were clear. There was no peripheral edema. Hemoglobin was 90 per cent (Tallqvist), and the erythrocyte count was 7,400,000. Orthodiascopic examination revealed an increase to +92 per cent deviation in the frontal area and +46.9 per cent deviation in the transverse diameter (Fig. 1). An electrocardiogram showed a persistence of the previous complete heart block, with marked right ventricular preponderance; in addition,  $T_1$  and  $T_2$  were low,  $T_3$  inverted, and  $T_4$  low and diphasic (Fig. 2).

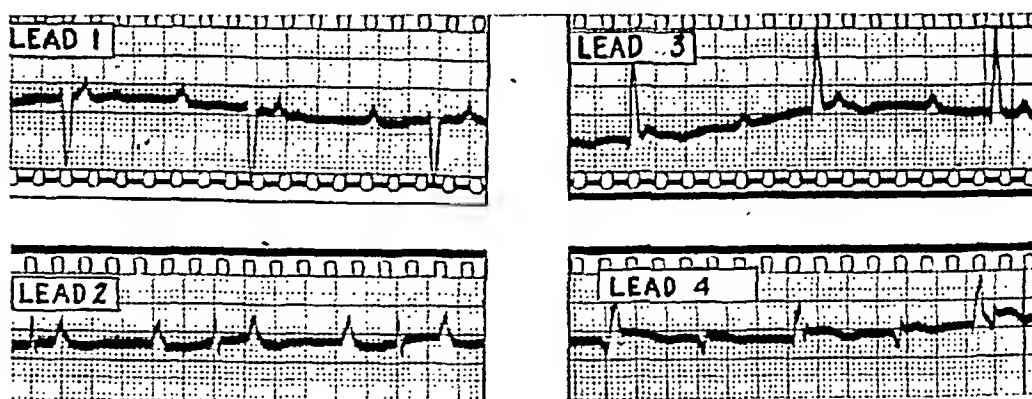


Fig. 2.

During the early portion of this terminal hospitalization, there was little change in the patient's condition, and she was able to be up and about the ward. A dental consultant advised complete extractions, but it was felt that only those teeth which had definite abscesses should be removed. Three days after the extraction of the lower central and lateral incisors she developed swelling and tenderness in the right cervical region. Several days later a similar condition was noted in the right upper extremity. It was believed that she had developed a thrombophlebitis of the right external jugular and right subclavian veins. Her course was rapidly unfavorable from this point, despite the administration of digitalis and oxygen. The venous pressure rose to 20 cm. of water, and 500 c.c. of blood were removed by venesection. Evidence of rapidly progressive decompensation developed, and the patient died two days after the signs of thrombosis of the right subclavian vein were noted. The hemoglobin rose to 100 per cent (Tallqvist), and the erythrocytes to 8,360,000, terminally.

*Autopsy Report.*—In addition to our general post-mortem examination, the heart was submitted to Dr. Maude E. Abbott, who very kindly examined it. Her report is included in the following.

On external examination, edema of the lower extremities and clubbing of the fingers and toes were found. The right arm and the right side of the neck were swollen and edematous, but no discoloration was noted here. There was cyanosis of the nails and mucous membranes.

Upon opening the pericardium, it was apparent that the position of the heart was abnormal, as the aorta lay anterior to the pulmonary artery. The organ weighed 450 Gm.

#### DR. ABBOTT'S REPORT ON HEART

*External View.*—The heart appears to have occupied its normal position in the thorax, but seems to have rotated somewhat on its own axis so that the left auricle lies toward the right posteriorly, entirely at the back of the heart. The ventricular part of the organ is a powerful muscular structure formed in two thirds of its extent by the right ventricle (as shown by the situation of the interventricular groove), and its apex, which points to the left and is broad and rounded, is formed entirely of the right chamber which curves upward on the left from below around the apex of the left ventricle, producing what may be described as the first degree of "coeur en sabot." The subepicardial fat is increased. The upper left border is very prominent, evidently representing the conus of the right ventricle, and from its extreme upper left angle emerges the transposed aorta in the position normally occupied by the pulmonary artery (Fig. 3). It passes directly upward to form the arch, from which the great vessels are given off in their normal position and relations.



FIG. 3.

Laid open, the aorta is a relatively small trunk, 5 cm. in circumference, just above the aortic valve, and it presents in its arch and thoracic portion some scattered calcified areas and atheromatous patches. Just opposite the origin of the left subclavian artery is a saccululation the size of a bean, in the floor of which are two calcareous plaques, and between these lies the pinpoint orifice of the ductus arteriosus which is a short trunk 1.2 cm. long, with obliterated lumen attached to the left branch of the pulmonary artery where it opens into the bottom of a small tent-shaped diverticulum by a minute opening admitting a bristle.

The pulmonary artery itself emerges transposed from the base of the ventricular portion of the heart on a plane posterior to and to the right of the aorta, which screens it on its left half, while on its right side it is hidden from the anterior view

by the greatly hypertrophied right auricular appendix, which stretches horizontally across it nearly as far as the root of the aorta. It is thin-walled and greatly dilated, with a lumen 8 cm. in circumference at its origin, increasing in size to 10 cm. at its bifurcation. The left auricular appendix is small and is entirely concealed from view anteriorly by the hypertrophied left border of the ventricle.

*Interior View.*—The right auricle is dilated to approximately three times the capacity of the left and is also hypertrophied, especially in the region of the large auricular appendix where the muscoli pectinati are of great size, and its chamber is expanded to the size of a tangerine. The foramen ovale is persistently patent, presenting a slit-like opening 1 cm. long, with thick fleshy borders. The annulus ovalis is present but not well developed. The eustachian and thebesian valves are both absent, and the mouth of the coronary sinus is represented by two small orifices, the lower of which opens into a small venous channel running in the auriculoventricular groove, while the upper leads into a vessel which runs up toward the back of the heart (pervious vein of Marshall?).



Fig. 4.

The tricuspid valve is supplied with three cusps, of which the marginal and infundibular appear normally formed. The "septal" segment, however, is a triangular flap attached at either border to small bundles of papillary muscles derived from the groups on either side, to which the other two cusps are attached, but which has no attachment to the free border of the defective interventricular septum, which lies to its left and posteriorly, presenting a huge defect some 2.5 cm. in diameter, which is screened from the blood entering the sinus of the ventricle from the auricle by the action of this septal cusp. (Fig. 4.)

The sinus of the right ventricle is a roomy chamber with hypertrophied walls, which enters into the formation of the apex and is separated from the left chamber by a muscular septum some 3.5 cm. high in its middle or lowest part, which curves upward at either end to become continuous with the left anterior and right posterior walls of the organ. The free upper border of this septum is a rounded muscular structure with chordae tendineae which are derived only from the mitral valve on the left side of the heart. The defect is bordered on its upper and anterior margin

by the crista supraventricularis of the right ventricle which separates it from the aorta, and on the left posteriorly by a tendinous structure below the transposed pulmonary orifice which apparently represents the aortic vestibule of the left ventricle, the lower border of which gives attachment to the chordae tendineae of the infundibular and septal tricuspid segments.

The upper portion of this right chamber is occupied by a rounded cavity the size of a walnut, demarcated below by a sharp muscular ridge, the right posterior wall of which is formed by the transposed aortic vestibule above mentioned and the base of the hyperplastic pulmonary cusps, and from it emerges the pulmonary artery guarded by two large, thickened cartilaginous and calcified cusps, the left anterior of which presents behind it a low raphe indicating a composite segment (Fig. 5). The sinuses behind these cusps are very deep (1.5 cm.), and take part in the tendinous posterior wall of this chamber.



Fig. 5.

The left auricle is of small size. It presents the crescentic free border of the valvula foraminis ovalis screening the patent foramen ovale and receives the openings of the pulmonary veins. The mitral valve has two normally formed segments, the left anterior of which is attached by its chordae to the free border of the defective ventricular septum and screens this from the lumen of the aorta which arises from the malposed pulmonary conus which has been placed in the growth of the heart on the left side of the ventricular septum, thus "correcting" the transposition that has occurred. There are three aortic cusps of about equal size, one posterior and two anterior, but the left anterior is the "free" cusp, the left coronary artery being given off behind the posterior segment and two right coronary arteries behind the right anterior.

*Anatomic Diagnosis.*—Transposition of the great trunks, with "correction" of this deformity by a huge defect of the interventricular septum (producing the effect of a cor biatriatum triloculare) and dextroposition of the transposed pulmonary artery, bringing this into the vicinity of the right auriculoventricular orifice, together with malposition of the pulmonary conus which lies contiguous to the mitral orifice and gives off the aorta. Persistent bulbus cordis forming a separate cham-



ber below the transposed pulmonary orifice. Bicuspid and hyperplastic pulmonic valve, with dilatation of the pulmonary artery above this. Hypoplasia and calcification of the aorta. Persistent patency of the foramen ovale. Hypertrophy and dilatation of the right auricle and ventricle, and hypertrophy of the left ventricle. Double right coronary behind right anterior cusp and left coronary behind posterior cusp. Persistent ligamentum arteriosum. (Fig. 6 is a schematic diagram indicating the foregoing mechanism.)

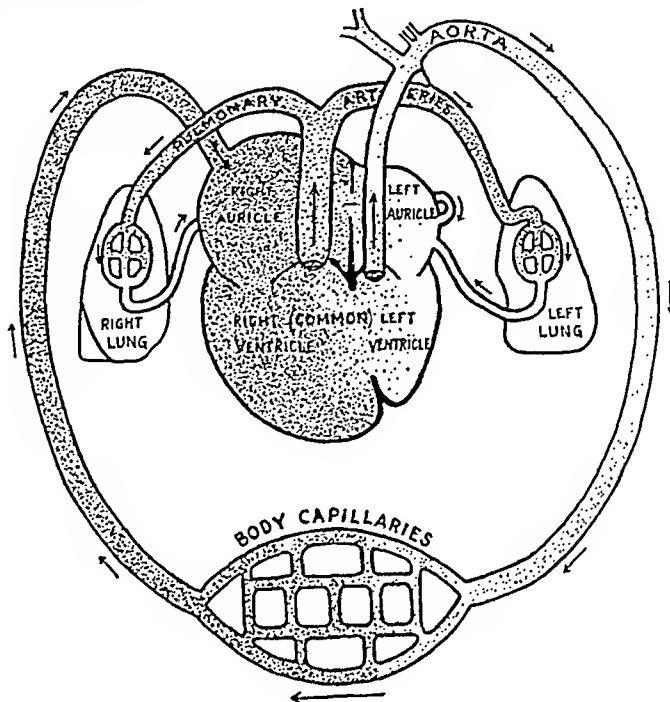


Fig. 6.

Chronic passive congestion of the liver, spleen, and kidneys; edema of the lower extremities; clubbing of the fingers and toes; edema of the right side of the neck and right upper extremity; localized pulmonary atelectasis; uterine polyps; simple cysts of right ovary; fibrous peritoneal adhesions (cause unknown).

Microscopic examination confirmed the gross diagnosis, with the following additional features: Pulmonary emphysema; acute lymphadenitis (bronchial lymph nodes); subacute hepatitis; biliary (obstructive) cirrhosis of the liver; chronic cholecystitis; chronic atrophic gastritis; acute endometritis; cystic changes in endometrium; chronic lymphadenitis (vertebral lymph nodes).

#### DISCUSSION

Abbott<sup>1</sup> reports six cases of corrected transposition in 1,000 cases of congenital heart disease analyzed. Of these, four are classified as primary lesions and two as complicating other defects. Only one of these persons reached the age of 24 years. She points out that corrected transposition is a rare and still incompletely understood phenomenon. Although Rokitsansky's brilliant hypothesis covered eight possible variations, only two of these had been observed by him. In this phenomenon a complete or crossed transposition has occurred, in that the great trunks arise in reversed relations, but the condition is "corrected" from the functional standpoint in that each trunk is placed in its proper ventricle.

In the case reported, the "correction" is accomplished in an unusual way, owing to the fact that the transposition itself is what Rokitansky would call "partial," that is, complicated by a huge defect in the septum. The complete heart block first demonstrated ten years before death is of further interest. It is quite possible that this condition was also congenital, as complete heart block is commonly associated with defects of the interventricular septum.

No record of a patient with this type of congenital heart disease who survived into the forty-fifth year has been found in the literature.

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## DISSECTING ANEURYSM OF THE AORTA

### CASE REPORT OF A NEGRO WITH AORTIC REGURGITATION AND SACCULAR ANEURYSM OF THE AORTA OF NONSYPHILITIC ORIGIN

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UNTIL the past few years dissecting aneurysm of the aorta has not been correctly diagnosed ante mortem save in rare instances.<sup>1-5</sup> There are two chief reasons for this tardy recognition of such a distinct pathologic entity: first, this syndrome has not received sufficient attention until recently; second, a sharply defined clinical pattern is often absent. The very nature of this disorder suggests that it should be accompanied by widely varied clinical manifestations. Thus, a single case often provides an inadequate conception of this syndrome as a whole, but may, as in the present case report, emphasize certain unusual aspects or associations. It is a study of these atypical cases which will advance our knowledge of the disorder.

H. R., a negro male, aged 58 years, was first seen by us in March, 1937, complaining of extreme shortness of breath. For the greater part of his life he had been well and strong despite the excessive strain attending his work as a court stenographer. For a number of years he was known to have had arterial hypertension, and in 1933 he began to complain of headaches, and undue dyspnea on exercise. Examination at that time revealed moderate cardiac enlargement and aortic regurgitation; the blood pressure was 220/90 mm. Hg. Although repeated serologic tests for syphilis were negative, he had been given antisyphilitic therapy over several periods of many months. In June, 1936, he was forced to stop work and since that time had developed increasingly severe headaches, weakness, and dyspnea. Roentgenologic examination in October, 1936, revealed moderate cardiac enlargement and aneurysmal dilatation of the aorta. An electrocardiogram showed marked left axis deviation and inversion of the T waves in Leads I and II.

Our examination revealed a well-preserved, rather thin, alert man, obviously dyspneic. The pupils reacted sluggishly but normally. The heart was greatly enlarged, the sounds were of poor quality, and gallop rhythm was present. At the aortic area a faint systolic murmur was heard, followed by a prolonged high-pitched diastolic murmur. The great vessel percussion dullness was markedly wider than normal. The blood pressure was 240/150. Moist râles were heard over the right lung base, but edema of the shins was not present. A diagnosis was made of hypertensive and probable syphilitic heart disease, with marked cardiac enlargement, slight aortic regurgitation, aneurysm of the aorta, and congestive failure.

Treatment with mercurial diuretics and digitalis resulted in improvement, and the patient passed a comfortable summer. On Sept. 17, 1937, he began to complain of darting pains in the chest. These pains were sharp and fleeting in character and were not related to exercise, excitement, or movement of the thorax. Nausea, shortness of breath, and anxiety were accompanying symptoms. These symptoms abated and examination two days later did not reveal any significant change. Fluoroscopic examination revealed marked cardiac enlargement and dilatation of

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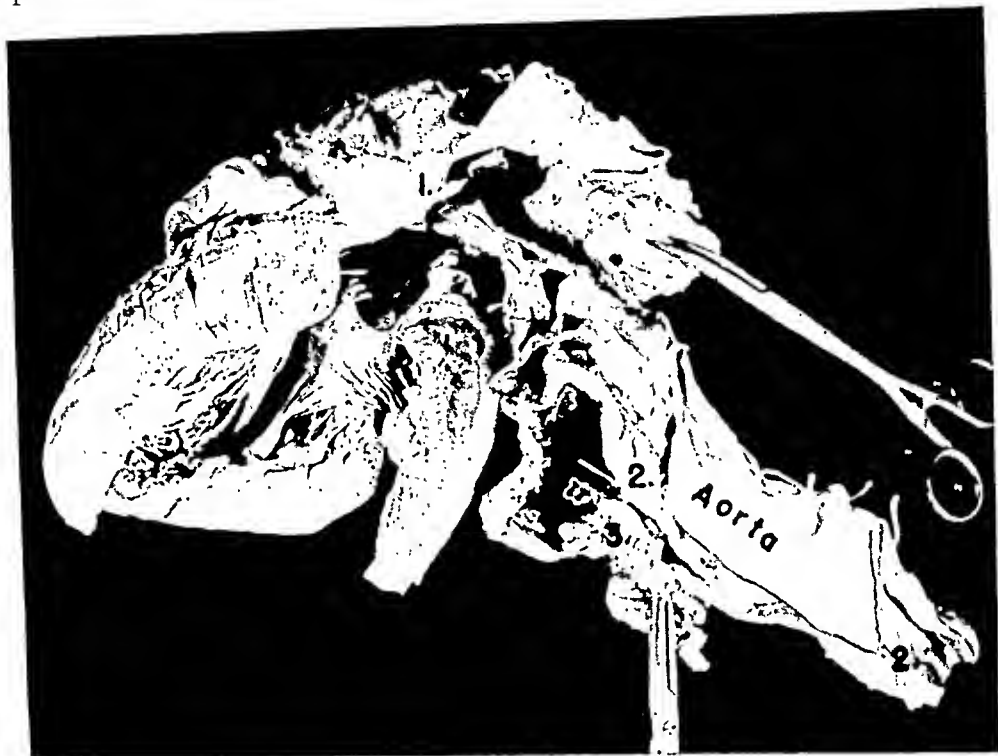


Fig. 1.—Photograph of the heart and aorta. 1, Original aneurysmal sac resulting from the initial dissection; 2, second aorta as a result of the original dissection; 3, sac resulting from the second perforation and showing the final perforation in its center.

At autopsy the left pleural cavity and posterior mediastinum were found to be filled with blood. The left lung was atelectatic save for the anterior half of the upper lobe. The right lung was atelectatic at the base. The heart weighed 600 Gm., the left ventricular wall measuring 25 mm., and the right 8 mm., in thickness. There was very slight thickening of the aortic valve cusps, and the valve opening measured 7 cm. in circumference. The coronary arteries showed only slight atherosclerosis. One of the smaller branches of the left coronary artery contained an old occluding thrombus, but an accompanying area of infarction was not present. The aorta was scarcely recognizable as such. Just proximal to the arch there was a smooth-edged opening through the intima 3 cm. in diameter leading into a large sac 8 by 6 by 4 cm. which extended back to the aortic ring and was partly filled with clotted blood. This sac was adherent to the pericardial surface of the right auricle and a separation between the two could not be made. The wall of the aneurysm was 2 to 4 mm. in thickness and was not only re-epithelialized but showed well-marked atheroma as well. The dissecting aneurysm extended also distally along the arch into the descending aorta and re-entered the left common iliac artery at a point 4 cm. beyond its origin. The dissection was not continued into the

branches of the arch but extended throughout the whole length of each renal artery and into the main branches of the celiac axis. Just above the diaphragm there was a fresh, ragged, oblique tear 1.5 cm. long in the outermost wall of the aneurysm which was the site of a second dissecting aneurysm. Thus, this dissection was in the adventitia of the wall of the original dissecting aneurysm. A third and final tear, at about the same level as the second, produced a rupture into the posterior mediastinal tissues and pleural cavity. Microscopic study of sections from various portions of the aorta did not reveal any evidence of syphilitic aortitis.

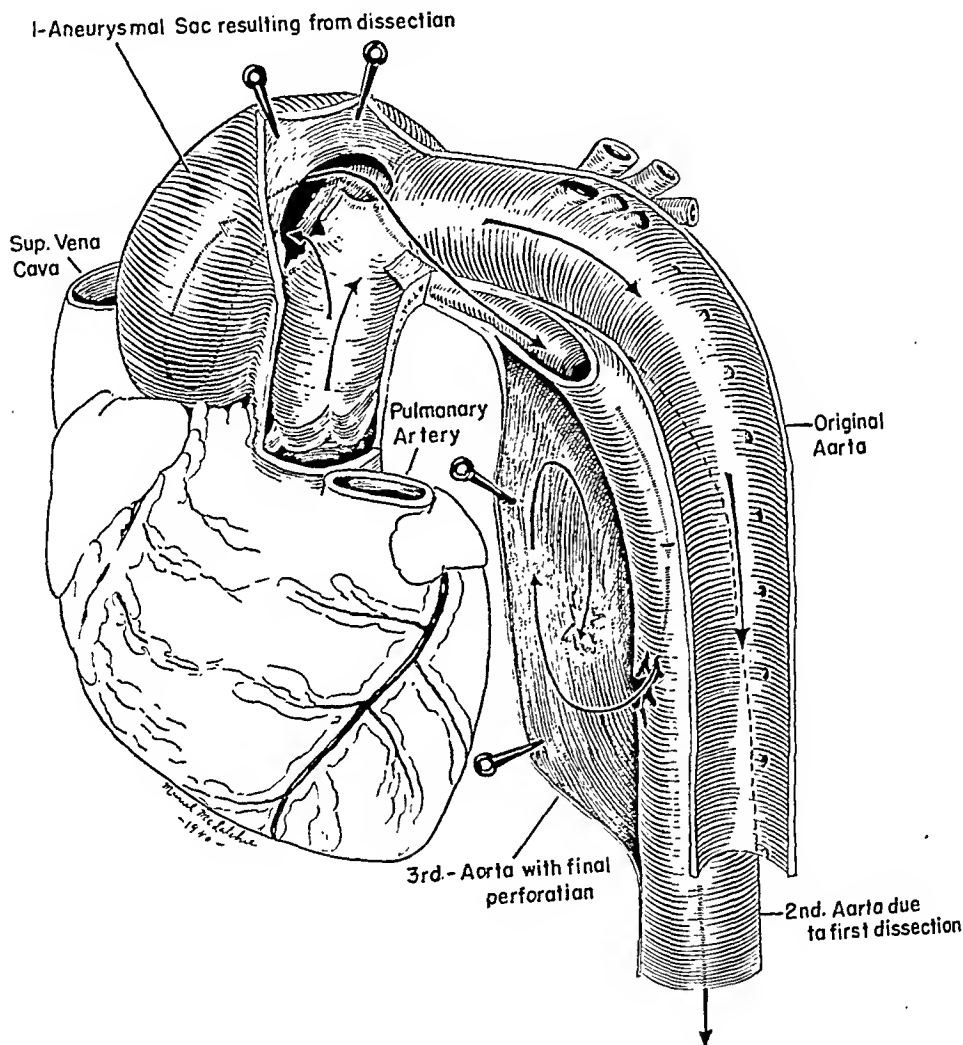


Fig. 2.—Sketch drawn from Fig. 1.

#### DISCUSSION

Whenever one is confronted with a problem in diagnosis, probabilities play an important role. Thus, given the case of a negro patient with aortic regurgitation, the probability of syphilis as the etiological factor is first considered. If, in addition, there is present a saccular aneurysm of the aorta, the diagnosis of syphilitic aortitis would seem highly probable, if not certain. In the present case these important signs were misleading and had resulted not only in the incorrect diagnosis of syphilitic aortitis but in extended antisiphilitic therapy as well.

Rarely, a dissecting aneurysm has led to the formation of a small saccular aneurysm and rarely aortic regurgitation has been noted as a clinical finding in such cases, but, heretofore, all three in combination have not been described. Only a few cases<sup>1, 2</sup> have been reported in which syphilitic aortitis and dissecting aneurysm coexisted, the pathologic nature of the former being such that it never leads to a dissecting type of lesion.

The original dissection in the present case must have occurred a year or more before death, to judge from the extent of the atheroma in the re-epithelialized portions. However, a history of significant chest pain was not obtained until the final episode. The only symptoms were those of congestive heart failure until shortly before death, when there were sharp fleeting pains in the chest and between the shoulder blades. Even this symptom was confusing because of the lung signs which suggested the possibility of pulmonary infarction. Nevertheless, the fall in blood pressure and the sudden exodus strongly suggested rupture of the aorta. Death might well have occurred at an earlier date due to congestive failure; in that case, the dissecting aneurysm would not have been an important factor in causing death.

This case emphasizes the fact that dissecting aneurysm of the aorta must be kept in mind in all cases of long-standing arterial hypertension. It may exist for years without apparent symptoms, and it may cause death under circumstances which make diagnosis difficult.

#### SUMMARY

A case is reported of a negro male, 58 years of age, with prolonged hypertension and dissecting aneurysm which occurred without any known history of severe chest pain. No evidence of syphilis was found at autopsy, and the Hinton reaction was negative. The original dissection had resulted in a rupture back into the lumen of the aorta, so that a double-barreled aorta was formed. This second aorta must have been present for a long time because there were atheromatous changes in the re-epithelialized surface. Death was due to a rupture and dissection into the adventitial space of the second aorta which, in turn, ruptured into the mediastinal space and pleural cavity.

Another case, having somewhat similar pathologic features (dissecting aneurysm of long duration, with sclerosis of the new aorta) and correctly diagnosed ante mortem, has been observed by Dr. Paul D. White.

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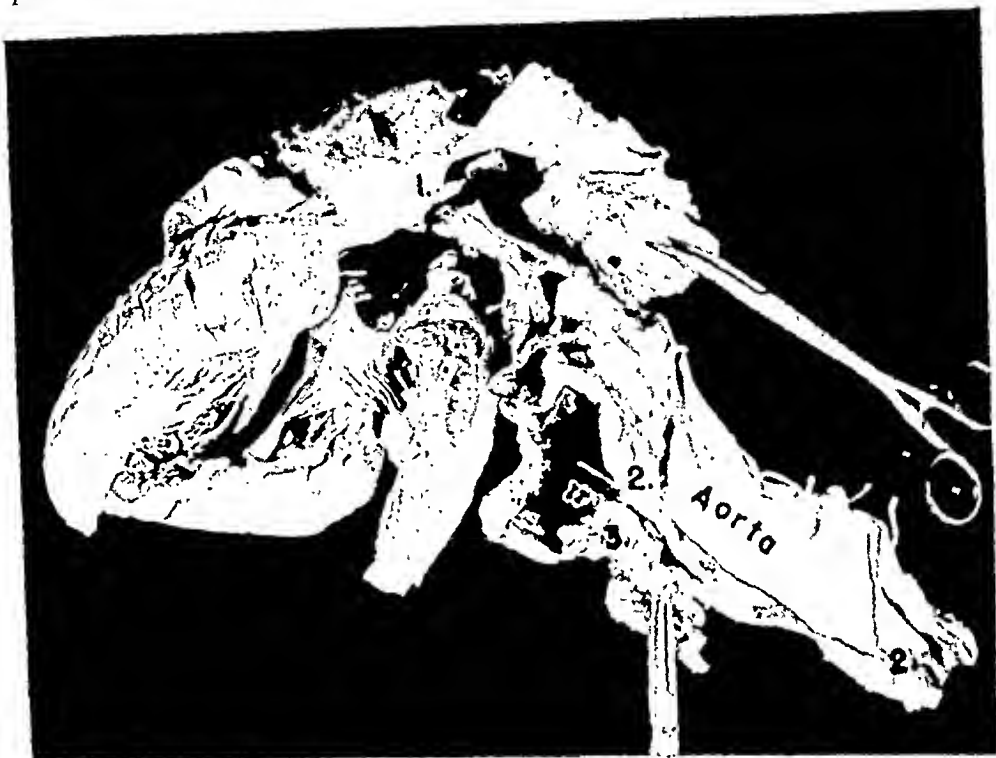


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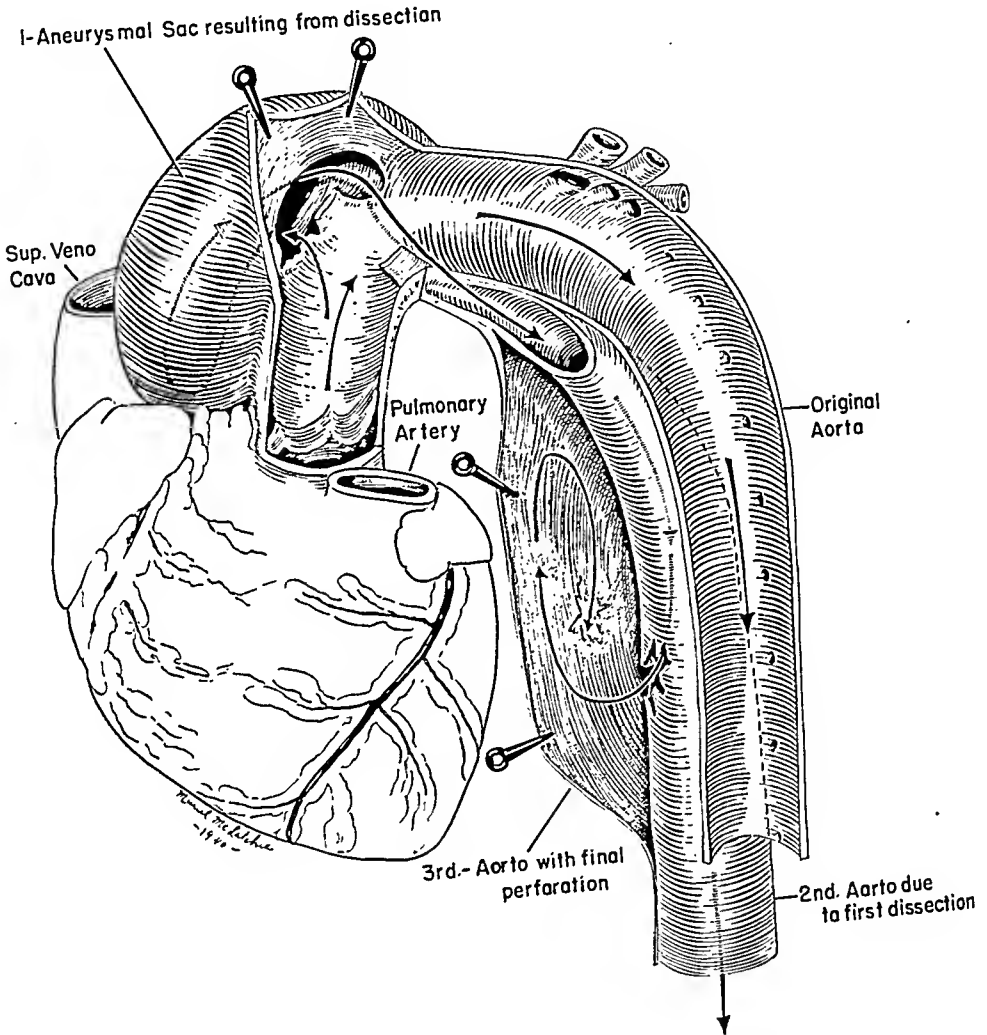


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# Department of Reviews and Abstracts

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## Selected Abstracts

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Smith, Lucian A., Allen, Edgar V., and Craig, Winchell McK.: Time Required for Blood to Flow From the Arm and From the Foot of Man to the Carotid Sinuses: I. Effect of Temperature, Exercise, Increased Intramuscular Tension, Elevation of Limbs, and Sympathectomy. *Arch. Surg.* 41: 1366, 1940.

The mean circulation time from the arm to the carotid sinus of normal persons in the present study was 20.1 seconds. The range was 12.4 to 33.2 seconds. The mean circulation time from the foot to the carotid sinus was 38.7 seconds. The range was from 22 to 67 seconds.

The temperature of the skin of the extremities and the circulation times from foot to carotid sinus and from arm to carotid sinus are closely related. Warmth of the skin decreases the circulation time, and coldness of the skin increases it.

Exercise of the legs, elevation of an extremity, lumbar sympathectomy, and increase of intramuscular tension caused by strychnine decrease circulation time in the part concerned.

NAIDE.

Smith, Lucian A., and Allen, Edgar V.: Circulation Time From Foot to Carotid Sinus and From Arm to Carotid Sinus of Man: II. Effects of Operation and of Administration of Thyroid Gland; Post-Operative Phlebitis and Pulmonary Embolism. *Arch. Surg.* 41: 1377, 1940.

Following a variety of surgical operations carried out under different anesthetic agents, it was found that the foot to carotid sinus circulation time is usually increased after the fourth day, that is, blood flows more slowly. Increases in the circulation time from the arm to the carotid sinus are less common and less marked. The slowing of venous circulation is probably an important factor in the complicated mechanism of postoperative venous thrombosis and pulmonary embolism.

Administration of thyroid gland to normal subjects decreases circulation time, that is, increases the rate of flow of blood from the arm and from the foot to the carotid sinus. Postoperative administration tends to prevent the slowing of venous circulation which commonly occurs after operation.

NAIDE.

Guttmann, E., and Jones, Maxwell: Hyperventilation and the Effort Syndrome. *Brit. M. J.* 2: 736, 1940.

Fifty-two cases of effort syndrome have been hyperventilated. In only 50 per cent of them were clinical symptoms reproduced in this way, and in these the symptoms were those which one commonly associates with tetany, e.g., paresthesia and disturbances of consciousness, rather than those characteristic of effort syndrome. We feel that, in view of our findings, we cannot support the contention of some workers that hyperventilation has an important place in the etiology of effort syndrome.

AUTHORS

Spillane, John D.: Observations on Effort Syndrome. *Brit. M. J.* 2: 739, 1940.

The group of patients who are diagnosed as suffering from the effort syndrome are psychoneurotics in whom somatic manifestations, in the cardiovascular sphere, are prominent. Psychologic difficulties are also present, but are frequently masked. There is no evidence that a fundamental physiologic defect is at work in the majority.

AUTHOR.

Bredt, H., and Stadler, L.: The Appearance of the Lesser Circuit in Inflammatory Heart Failure and Its Significance in the Clinical Picture. *Arch. f. Kreislauf-forsch.* 7: 54, 1940.

Thirty-seven cases of rheumatic heart disease with valvular involvement were the basis of the study. Pulmonary vessels were examined microscopically. Involvement was noted in the arteries, arterioles, and veins and consisted of inflammatory reactions, proliferation of intima, encroachment of the lumina, and disappearance of media. These changes are attributed to the same processes as those causing the endocarditis. These pulmonary endarteritides are thought to contribute to the clinical picture, especially the cyanosis and dyspnea.

KATZ.

Morelli, Alberto C.: Extra Rapid Tomography in the Examination of the Circulatory Apparatus. *Rev. argent. de cardiol.* 7: 217, 1940.

A modification of the method of Vallebona and Bozetti is described for extra-rapid tomography applicable to the radiologic study of the heart, pulmonary vessels, and mediastinum.

The modifications consist in the employment of very deep rays in reduced areas and in the kind of movement which the patient undergoes.

During the first half of the run the movement is progressively accelerated, and during the second half it is symmetrically retarded. The x-ray picture is obtained during the end of the first and the beginning of the second half period.

With this system, since the angular velocity is greater at the center of the angle in which the picture is obtained, the amount of x-rays which the body receives at the lateral limits of the angle will be greater, the dispersion effect in those planes out of focus will also be greater, and, therefore, the tomographic effect will be better the smaller the angles of displacement.

These extrarapid tomographies (exposures of 0.03 to 0.1 second) are clearer (a) the smaller the angle of the run, (b) the shorter the time of exposure, (c) the greater the difference in velocity between beginning and end of the rotation movement (when the velocity is smaller) and the center of the run where the velocity is greater, and (d) the greater the penetration of the x-rays. There are other minor factors, such as focus of the x-ray tube, distances, tube-film, and patient-film, mechanical vibrations, etc., which may be important.

AUTHOR.

Peet, Max Minor, Ward, Wilson Woods, and Braden, Spencer: The Surgical Treatment of Hypertension. *J. A. M. A.* 115: 1875, 1940.

Three hundred and fifty consecutive cases of hypertension with operation by bilateral supradiaphragmatic splanchnicotomy and lower dorsal sympathetic ganglionectomy have been studied over a period of nearly seven years.

Of the patients studied, 86.6 per cent had postoperative relief of major symptoms, especially headache, 81.3 per cent had improvement or complete relief of incapacita-

tion, and 51.4 per cent with adequate postoperative data had a significant reduction in blood pressure. In approximately one-half of these patients pressures fell to normal or were markedly reduced.

Improvement in ophthalmologic, cardiac, and renal status following operation occurred in from 45 per cent to 70 per cent of the cases studied.

Prognosis was much more favorable in females than in males.

The most favorable results were obtained in the age group before 30. Following this period age appeared to be of minor importance.

Far-advanced fundus changes, i.e., marked angiospasm and papilledema, were not contraindications to the operation.

The operative mortality was low (3.4 per cent), and no specific ill effects were attendant on the operation.

Finally, no other form of therapy, whether medical or surgical, which offers such good results in patients suffering from hypertension of an equal degree of severity has, as yet, been reported. Furthermore, these results are not temporary but continue over a period of years.

The conclusion is reached that the surgical treatment of hypertension by bilateral supradiaphragmatic splanchnicotomy and lower dorsal sympathetic ganglionectomy offers a better prognosis in cases of severe hypertension than any other form of therapy as yet reported.

NAIDE.

**DeTakats, Geza, and Scupham, George W.: Revascularization of the Ischemic Kidney. Arch. Surg. 41: 1394, 1940.**

Four hypertensive patients in whose cases the diagnosis of malignant nephrosclerosis was made were operated on with the idea that the ischemic kidney might obtain some additional circulation. The kidneys were decapsulated; the cortex was incised; and the omentum or a pedicled muscle flap was wrapped around the kidney. The four case reports are summarized. One patient has been followed for three and one-half years. In no patient was there a definite improvement. It is possible that, if patients with essential hypertension with earlier or more proximal vascular damage were subjected to such a procedure, the condition might be arrested or improved. The importance of taking renal biopsy specimens and the difficult interpretation of biopsy observations in the early stages are emphasized. For the late stages in which the patient is referred to the surgeon, renal vascularization has been of no value.

NAIDE.

**Moss, H. K., and Herrmann, L. G.: Use of Quinine for Relief of "Night Cramps" in the Extremities. J. A. M. A. 115: 1358, 1940.**

Fifteen patients who suffered from "night cramps" were treated successfully with quinine sulfate. It is thought that quinine acts on the myoneural junction and may be the antagonist of prostigmine.

SCHWARTZ.

**Fetter, Ferdinand, and Schnabel, Truman G.: The Behavior of the Blood Sedimentation Rate During and After Fever Therapy. Am. J. M. Sc. 201: 115, 1941.**

Sedimentation rates were determined on forty-one patients who were receiving physically induced fever in the hypertherm. Determinations were made before, during, immediately after, and the day after the fever treatment.

No significant variations in the sedimentation rates were found in these four determinations.

For practical purposes, physically induced fever used therapeutically does not affect the sedimentation rate.

An accurate determination of the sedimentation rate can, therefore, be made at any time during or after a fever session.

AUTHORS.

**Gammon, George D., and Starr, Isaac, Jr.:** Studies on the Relief of Pain by Counterirritation. *J. Clin. Investigation* 20: 13, 1941.

After inducing pain on themselves by the subcutaneous injection of 10 per cent NaCl or the application of irritant ointments, the authors studied the relief brought by counterirritation of various types, e.g., heat, cold, the electric current, vibration, and tactile stimulation.

Irrespective of the type of pain and counterirritant, a definite pattern usually appeared; the application of counterirritation caused temporary relief; its removal was also followed by temporary relief.

Experiments demonstrated that the relief secured was not due to changes in the circulation. Animal experiments in which the discharge from sensory nerves was recorded yielded results which are analogous to some of the changes of sensation experienced. On the other hand, other changes of sensation could not be accounted for by an altered sensory discharge. We have discussed the possibility that they are due to a central depression of the pain.

As periodic counterirritation produced the maximum of relief of pain induced in the authors themselves, apparatus was devised for the intermittent application of heat and cold to patients.

While there is great difficulty in judging the effectiveness of agents acting on the sensation of patients, we have gained the impression that by wise selection and periodic application of counterirritants much more relief can be secured than by the haphazard application of hot water bottles and ice bags which was our former practice.

AUTHORS.

**Castleden, L. I. M.:** The Effect of Potassium Salts on Cardiac Irregularities. *Brit. M. J.* 1: 7, 1941.

The administration of potassium salts caused the disappearance of extrasystoles in one case in which they were associated with insulin hypoglycemia and in four in which they were spontaneous.

In three of these five cases the level of potassium in the serum was estimated, and the disappearance of the extrasystoles was associated with a rise in potassium level.

Attempts to produce extrasystoles by the administration of ephedrine were not successful. In contrast with insulin and adrenaline, ephedrine does not produce consistently a fall in the serum potassium.

Potassium salts have been reported to produce cardiac irregularities in experimental animals and to increase the incidence of extrasystoles and paroxysmal tachycardia in some patients, so that their action in suppressing extrasystoles cannot be utilized with confidence in the treatment of patients until further work has clarified the mechanism of these effects.

AUTHOR.

Glyn-Hughes, F., and Spence, A. M.: Sulphonamide Therapy in Lupus Erythematosus. *Brit. M. J.* 2: 741, 1940.

There was a definite response to sulfonamide therapy in each of the twelve cases cited, a point which strongly supports the theory of a streptococcal origin of the disease. In fact, even among the failures some of the chronic sufferers were very loath to abandon the treatment because of the hopes to which the initial success had given rise. Six patients, or 50 per cent, were completely healed and have remained so. The existence of some latent and resistant focus of infection is the probable cause of failure in the other cases. One patient relapsed twice, but, after a previously overlooked cervical erosion had been treated, she was completely cured.

The successful cases included all those patients who had not suffered from the disease for more than a year. When it is considered that roughly 25 Gm. of sulfonamide administered over a period of about four weeks has been successful in clearing up what is regarded as an intractable disease, the effect of the drug appears well-nigh specific and suggests that the prognosis in early cases is very favorable.

AUTHORS.

Wolff, H. G., Hardy, J. D., and Goodell, H.: Measurement of the Effect on the Pain Threshold of Acetylsalicylic Acid, Acetanilid, Acetophenetidin, Aminopyrine, Ethyl Alcohol, Trichlorethylene, a Barbiturate, Quinine, Ergotamine Tartrate, and Caffeine: An Analysis of Their Relation to the Pain Experience. *J. Clin. Investigation* 20: 63, 1941.

Quantitative measurements of the pain threshold were made by irradiating 3.5 sq. cm. of skin surface for three seconds. The intensity of radiation which barely evoked pain was denoted as the pain threshold. The threshold-raising action of various nonopiate analgesic agents was then ascertained in terms of the normal threshold.

Acetylsalicylic acid (oral) in quantities of 0.03 Gm. to 1.8 Gm. was thus assayed. The minimum effective quantity of this agent is 0.06 Gm. (0.9 mg. per kilogram of body weight). The "saturation" quantity or the smallest amount with which the highest threshold-raising effect was attained was 0.3 Gm. The highest threshold-raising effect of which the agent was capable was approximately 35 per cent above the control threshold, and the maximum threshold-raising effect for quantities of acetylsalicylic acid, in amounts of 0.06 Gm. to 1.8 Gm., was attained in approximately 50 to 100 minutes.

The time-action curves of threshold-raising effect for acetylsalicylic acid revealed that essential elimination increased at a constant rate with quantities up to 0.3 Gm. However, with larger quantities of the agent, there was acceleration of the essential elimination rate so that durations of effect with 0.9 Gm. and 1.8 Gm. differed but slightly.

The pain threshold-raising action of 0.3 Gm., respectively, of acetanilid, acetophenetidin, and aminopyrine were measured. In these amounts these agents had time-action curves similar to that obtained with 0.3 Gm. of acetylsalicylic acid.

Acetylsalicylic acid induced mild relaxation and lethargy. Acetanilid and acetophenetidin in comparable amounts induced greater relaxation and lethargy and difficulties in mentation. The therapeutic effectiveness of the latter agents rests in good part on their effects.

The pain threshold-raising actions of 30 c.c. and 60 c.c. of ethyl alcohol (oral) were measured. In these amounts the alcohol had a maximum threshold-raising action of 40 per cent above the control level. The larger amount had a longer duration but no greater threshold-raising action.

The pain threshold-raising action, as well as other observable effects, of acetylsalicylic acid, acetanilid, acetophenetidin, and ethyl alcohol was relatively slightly reduced by pain. A uniform pain stimulus was introduced just before or during the first sixty minutes after administration of the agents. Thus, the antagonism between pain and threshold-raising action noted in the case of the opiates is less evident or absent in the case of the above-mentioned agents.

Some effects of alcohol were akin to those of the opiates. Of special significance in both were the emotional states referred to as freedom from anxiety and feelings of contentment and detachment. While in these states, the subjects perceived pain, but they were indifferent to it. Thus like the opiates but perhaps to a lesser degree, alcohol accentuates the ability to dissociate pain perception from the pattern of reaction to pain.

The pain threshold-raising action of 1 c.c. of trichlorethylene (inhaled) was measured. It had a maximum threshold-raising action of approximately 40 per cent above the control level.

The pain threshold-raising action of 0.5 Gm. of the sodium salt of N-methylecyclohexenylmethyl barbituric acid ("Evipal" brand) was measured. It had a maximum threshold-raising action of approximately 20 per cent above the control level and induced profound lethargy and defects in mentation.

Caffeine sodiobenzoate, ergotamine tartrate, and quinine sulfate had no pain threshold-raising properties.

Various combinations of acetylsalicylic acid, codeine, acetanilid, acetophenetidin, the barbiturates, and caffeine were studied. The pain threshold-raising effect of any combination was no greater than that of its most effective ingredient. Sedative and hypnotic effects, as well as defects in motility, seemed to be summative. A combination of these agents is therapeutically valid if it aims to attain useful psychologic effects coupled with pain threshold-raising action. It is not valid, however, if it be assumed that the pain threshold-raising effects of the different ingredients will summate.

AUTHORS.

Davis, Loyal, and Barker, M. Herbert: The Depressor Effect of Potassium Sulfo-cyanate Before and After Bilateral Splanchnicotomy in Normal and Hypertensive Dogs. *J. Lab. & Clin. Med.* 26: 658, 1941.

From the results of acute experiments carried out upon normal dogs, ischemic hypertensive dogs, and normal dogs with elevated blood cyanate levels, it would seem logical to believe that the effect of the intravenous injection of potassium sulfocyanate produces its depressor effect as the result of a general vasodilatation. This effect can be increased by removal of the thoracic sympathetic trunk and splanchnic nerves supradiaphragmatically. These experimental observations lend support to the observation made clinically that in many instances patients who respond poorly to cyanate therapy may become sensitive following a bilateral splanchnicotomy.

AUTHORS.

Page, Irvine H., Helmer, O. M., Kohlstaedt, K. G., Fouts, P. J., and Kempf, G. F.: Reduction of Arterial Blood Pressure of Hypertensive Patients and Animals With Extracts of Kidneys. *J. Exper. Med.* 73: 7, 1941.

Extracts of kidneys containing a substance which lowers arterial blood pressure for prolonged periods in patients with essential and malignant hypertension and in hypertensive dogs and rats have been prepared.

Several different chemical procedures are proposed for the preparation of the extract. The best one has not been determined.



The quantity of original fresh whole kidney required to yield enough extract to lower blood pressure from hypertensive levels (200 mm. Hg mean pressure) to normal levels is roughly 600 to 900 Gm. in dogs within four to eight days. In hypertensive patients the yield of 700 to 1,000 Gm. daily for several weeks may be necessary.

Lowering of the blood pressure too rapidly in animals results in a shock syndrome which may be fatal. If overdosage is avoided, no appreciable rise in blood urea nitrogen occurs, nor do other signs of toxicity appear.

Lowering of blood pressure to nearly normal levels has been accomplished in sixty hypertensive dogs, and in some of these the blood pressure was allowed to rise and was again reduced as many as five times. Similar results have been obtained with hypertensive rats.

The effect of treatment on six patients with essential hypertension was prolonged reduction of blood pressure. Clinically the patients appeared improved.

Five patients with malignant hypertension have been treated, with reduction of the blood pressure in all instances. One patient was treated despite urea clearance of 5 per cent of normal. His blood pressure was sharply reduced, but death caused by uremia occurred. The second patient also exhibited sharp reduction of pressure and diet after treatment was discontinued. The other three were much improved after treatment, as indicated by increase in vision and mental activity, loss of dyspnea, improvement in the electrocardiogram, etc.

The length of time the blood pressure remains lowered varies greatly in both animals and man. The trend is usually upwards after treatment has been discontinued for four to six days.

Increasing experience with this treatment suggests that it is of value in the management of hypertension, but it is still in the experimental stage.

AUTHORS.

Wang, S. C., and Ranson, S. W.: The Role of the Hypothalamus and Preoptic Region in the Regulation of Heart Rate. *Am. J. Physiol.* 132: 5, 1941.

The typical rise and afterfall in the plasma potassium concentration following epinephrine injection have been confirmed in the dog and have been found to be present in sheep and goats.

The active uptake of potassium by the muscles in this connection has been confirmed in dogs.

In the hind limbs of the frog perfused with gum acacia-Ringer the uptake of potassium from the perfusion fluid has been found to be independent of the rate of flow. Epinephrine has not been found to have a direct effect.

The hind limbs of the frog similarly perfused and indirectly stimulated nine times per minute have been found to lose potassium at the rate of 0.5 to 0.6 gamma of potassium per gram of hind limb per minute.

If a constant perfusion of epinephrine is used with the stimulated muscles, it has been found to reduce the rate of potassium loss by 40 per cent.

AUTHORS.

Mendlowitz, Milton: Measurements of Blood Flow and Blood Pressure in Clubbed Fingers. *J. Clin. Investigation* 20: 113, 1941.

The Stewart method for measuring blood flow has been shown to be accurate when applied to the finger tip.

The normal range of variation of blood flow and brachial-digital pressure gradient, after release of sympathetic tone, has been determined.

In essential hypertension, aplastic anemia, hyperthyroidism, acromegaly, and diverse chronic infections, all without clubbing, the blood flows and pressure gradients were within the normal range.

In all the varieties of simple clubbing studied, except hereditary clubbing, the blood flows per unit surface or volume of finger tip were abnormally high. These excessive flows were caused, in part at least, by elevated digital arterial pressures. Since the brachial-arterial pressures were unchanged, the brachial-digital gradients were reduced. After incision and drainage of a lung abscess, the previously increased blood flow and digital-arterial pressure returned to normal with recession of the clubbing. It is therefore apparent that abnormally high blood flow and digital-arterial pressure after release of sympathetic tone are peculiar to ordinary clubbing and integral forces in its development. In hereditary clubbing the normal blood flow per unit of tissue and the normal pressure values found indicate that the mechanism of clubbing here is different from that which operates in the ordinary cases.

In hypertrophic osteoarthropathy the blood flow per unit of tissue and the digital-arterial pressure were within normal limits. Since the mean digital-arterial pressure can never be higher than the mean brachial, the increase in digital-arterial pressure, and hence in digital blood flow in simple clubbing without bone changes, is limited. As the circulatory derangement associated with clubbing advances, therefore, it is possible that there is a recession or at least a stabilization of the phenomenon in the finger tips and that the process of increased blood flow and hypertrophy is taken over by the bones.

AUTHOR.

Castex, Mariano R., Battro, Antonio, and González S, Robert: *Diagnosis of the Site of Origin of Ventricular Extrasystoles in Human Beings*. *Arch. Int. Med.* 67: 76, 1941.

Electrocardiograms and phonocardiograms registered simultaneously with tracings of central arterial or venous pulse allow us to prove asynchronism of ventricular contraction and also to determine which of the ventricles contracts first.

In this manner we have studied twenty-three cases of spontaneous extrasystoles in human beings (ten showing negative deflection and thirteen, positive deflection in Lead I), and we have been able to determine to which ventricle corresponds the priority in contraction.

When extrasystole occurs with a negative deflection in Lead I, the data obtained show that the left ventricle contracts before the right one.

When extrasystole occurs with a positive deflection in Lead I, the manifestations of asynchronism show priority of contraction in the right ventricle over that in the left one.

Because of the facts stated, we consider ourselves justified in concluding that premature beats with negative deflections in Lead I originate in the left ventricle and those with positive deflections in Lead I, in the right ventricle.

AUTHORS.

Friedman, Meyer, Selzer, Arthur, and Rosenblum, Harold: *The Renal Blood Flow in Coarctation of the Aorta*. *J. Clin. Investigation* 20: 107, 1941.

The effective renal blood flow and the rate of glomerular filtration were measured by means of the diodrast and inulin clearances, respectively, in a group of eleven normal control subjects and in a group of six patients with coarctation of the aorta.

The findings in the cases of coarctation indicated an appreciable decrease in renal blood flow as compared to the normal subjects. The glomerular filtration rate, however, was normal.

The arterial hypertension in coarctation is interpreted in the light of primary reduced renal blood flow associated with secondary glomerular efferent arteriolar spasm. A probable relationship of these factors to the pathogenesis of essential hypertension is pointed out.

AUTHORS.

Garvin, Curtis F.: Mural Thrombi in the Heart as a Source of Emboli. *Am. J. M. Sc.* 201: 412, 1941.

In 771 consecutive adult autopsied patients who died of heart disease, pulmonary infarction was almost three times as frequent in those cases with mural thrombi in the right side of the heart as in those cases without. Infarcts of the brain, kidneys, spleen, intestines, and/or extremities were more than twice as common in cases with mural thrombi in the left side of the heart as in their absence. A similar relationship was found to exist in regard to hypertensive heart disease, coronary artery disease with or without myocardial infarction, and rheumatic heart disease, with one exception. In coronary artery disease without myocardial infarction, infarcts in the brain, kidneys, spleen, intestines, and/or extremities were 1.7 as frequent when mural thrombi were present in the left side of the heart as in their absence, but the difference was not statistically significant. This exception may be due to the small size of the series and/or to the fact that these cases showed considerable peripheral vascular disease which no doubt increased the incidence of infarction due to thrombosis in situ. These observations indicate that mural thrombi in the heart are a significant cause of embolic occlusion of arteries in both the lesser and greater circulations.

AUTHOR.

Hutcheson, William C.: An Anatomic Basis for Auricular Fibrillation. *Arch. Path.* 31: 369, 1941.

It is believed that auricular fibrillation in patients with chronic rheumatic heart disease may be due to substitution of auricular smooth muscle for striated cardiac muscle.

AUTHOR.

Baggenstoss, Archie H., and Rosenberg, Edward F.: Cardiac Lesions Associated With Chronic Infectious Arthritis. *Arch. Int. Med.* 67: 241, 1941.

In a study at necropsy of twenty-five cases of chronic infectious (rheumatoid) arthritis, cardiac lesions were demonstrated in twenty. Lesions identical with those of rheumatic fever were observed in fourteen (56 per cent). Nonrheumatic cardiac lesions were present in six (24 per cent). In ten of the fourteen cases in which there were rheumatic lesions there was histologic evidence that the inflammatory process was still active and progressive at the time death occurred. In seven of the fourteen instances associated with rheumatic cardiac lesions, the heart disease was judged to be an important factor in causing death. In only seven of the fourteen instances associated with rheumatic cardiac lesions had signs or symptoms of heart disease been present during life. The high incidence of rheumatic cardiac lesions in this series is suggestive of a relationship between chronic infections (rheumatoid) arthritis and rheumatic fever.

AUTHORS.

Kahn, Joseph R., and Ingraham, Edgar S., Jr.: **Cardiac Hypertrophy and Coronary Arteriosclerosis in Hypertension.** *Arch. Path.* 31: 373, 1941.

Within the limitations of this sort of statistical study, the results suggest that arteriosclerosis of the coronary arteries may play a part in the genesis of cardiac hypertrophy in patients with prolonged hypertension.

AUTHORS.

Katzenstein, Rolf, and Murphy, James Peter: **Acute Sclerosing Vascular Disease With Renal Changes.** *Arch. Int. Med.* 67: 579, 1941.

An unusual case of vascular disease, occurring in a 22-year-old woman, is presented. Sclerosing changes in small arteries, without thrombosis, characterized the vascular lesions. The cause of the condition is entirely unknown. Clinically, the illness simulated bilateral renal cortical necrosis. Arteriolar lesions (with subsequent cerebral injury) were noted, and their possible pathogenesis is discussed.

AUTHORS.

Burrett, John B., and Scherf, David: **The Clinical Importance of Small Intracutaneous Veins in the Human Chest.** *Am. J. M. Sc.* 201: 399, 1941.

Ectasia of small intracutaneous veins located in the neighborhood of the pleural sinuses is described. An examination of 385 patients revealed that the appearance of these veins is not the result of pulmonary, pleural, or cardiac disease. They are found in healthy people. Their incidence increases with age. An explanation of their developmental mechanism is offered.

AUTHORS.

Steinbrocker, Otto, and Samuels, Saul S.: **The Arterial Circulation of the Lower Extremities in Chronic Arthritis.** *J. Lab. & Clin. Med.* 26: 974, 1941.

In a clinical investigation of rheumatoid arthritis, 65.9 per cent of the patients showed abnormalities, usually vasomotor disturbances, of the arterial circulation of the lower extremities; in osteoarthritis 35.2 per cent of the cases presented similar findings. Three rheumatoid patients, or 6.3 per cent had simultaneous arteriosclerotic occlusive disease; two with osteoarthritis, or 2.8 per cent, presented evidence of arteriosclerosis obliterans.

Study of those patients with arthritis presenting arterial abnormalities showed no direct, consistent relationship between the location of the vascular signs and the site of the arthritic process. The evidence suggests that the vasomotor disturbances in chronic rheumatoid arthritis and related conditions may be attributed to some systemic reaction probably acting through the sympathetic nervous system, although in some cases a local irritative reflex vasospastic mechanism in the painful arthritic extremity cannot be ruled out.

In a control group of eighty-six patients with advanced organic arterial disease twenty-eight, or 32 per cent, offered a history, physical signs, or roentgen changes of rheumatic or arthritic involvement at some time. These findings approximate the incidence of such ailments in similar age groups of persons without arterial disturbances and contribute clinical evidence that pronounced arterial disease alone does not usually produce arthritic signs and symptoms.

AUTHORS.

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\**Executive Committee.*

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## Original Communications

### PROPHYLAXIS AGAINST LETHAL EFFECT OF HIGH ALTITUDE BY MEANS OF A DIGITALIS GLYCOSIDE (GITALIN)

ERNST FISCHER, M.D.  
RICHMOND, VA.

IN THE course of a comprehensive investigation concerning the relation between drug susceptibility and high altitude, the remarkable prophylactic action of gitalin against the lethal effect of the severe anoxia produced by high altitude became evident. Since this protective action of digitalis might be of some importance in aviation medicine, the experimental data on this prophylactic effect are presented now, without waiting for the complete results of the originally planned investigation.

#### METHODS

Male mice (from the same colony) which weighed 15 to 20 Gm. were used. For each experiment thirty mice of approximately equal weight ( $\pm 3$  Gm.) were divided into two groups of fifteen, each of equal weight distribution. A 0.1 per cent gitalin solution was prepared by dissolving the gitalin in as little 95 per cent alcohol as possible, and then diluting the alcoholic solution with Tyrode solution to the desired volume. Of the final solution, amounts containing 2.5 to 10.0 gamma\* per Gm. were injected intraperitoneally into the members of one of these groups. In preliminary experiments the L. D.<sub>50</sub>† was established at about 50 gamma per Gm. Both groups, the protected and the control, were kept under identical conditions (for four to seventy-two hours), and later exposed simultaneously to low pressure in a big glass desiccator used as a decompression chamber, simulating altitudes between 30,000 and 34,000 feet. Accumulation of carbon dioxide was avoided by using a pump capable of maintaining the desired pressure despite an adequate air flow. Decompression was produced gradually and as uniformly as possible. A pressure corresponding to 22,000 feet was reached in three minutes, and the final altitude in the next three minutes. Return to normal pressure occurred in a corresponding way. The duration of the exposures as given in the tables includes not only the time the final pressure was maintained, but also half of the time during which the pressure changed from that of 22,000 feet to the final altitude, or vice versa. Despite all of the care that was taken to perform the experiments as

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\*1 gamma =  $\frac{1}{1000}$  mg.

†The dose per gram which is fatal to 50 per cent of the animals given that amount.

uniformly as possible, the susceptibility of the mice to high altitude varied very much from one experiment to another. Apparently, the age of the mice, their average weight, and the humidity and temperature of the atmosphere are factors influencing the high altitude susceptibility. However, in simultaneous experiments with two uniform groups of mice or with a normal group and a group of mice which had received in advance 0.01 c.c. per Gm. of Tyrode solution intraperitoneally, the difference in mortality was small ( $\pm 4.2$  per cent). Therefore, the difference in mortality which was observed between the gitalin group and the control group of each experiment was more or less a measure of the protection afforded. If twelve died in the control group, and only six in the protected group, the actual protection was 50 per cent. However, a simple consideration demonstrates that this actual protection percentage does not mean much, since it depends to a certain extent on the duration of the exposure. If, in the same experiment, the exposure had been much shorter, the result could have been one death in the control series and no death in the protected group, which would be an actual protection of 100 per cent. With increased duration of exposure, the result could have been fifteen fatalities in the control series and any number between six and fifteen fatalities in the protected group. However, with a reasonable degree of

TABLE I

GITALIN PROPHYLAXIS AGAINST LETHAL EFFECT ON HIGH ALTITUDE.  
DEPENDENCE OF PROBABLE PROTECTION FACTOR ON ALTITUDE

EXP. NO.	DOSE GAMMA PER GRAM	INTERVAL BETWEEN PROPHYLAXIS AND EXPOSURE HOURS MIN.		EXPOSURE		DEATH RATIO		PROBABLE PROTECTION FACTOR*
				FEET	TIME MIN.	CONTROL	PROTECT.	
D 20	5.0	23	18	30,000	17	11/15	3/15	56.3
D 21	10.0	23	36	30,000	62	4/15	1/15	47.5
D 24	5.0	24	12	30,000	30	11/15	6/15	43.9
mean	5-10	23	42	30,000	36	26/45	10/45	48.5
D 1	2.5	26	20	30,000	25	6/15	2/15	23.3
D 2	5.0	4	22	32,000	15	9/15	3/15	53.3
D 7	5.0	8	0	32,000	23	3/15	0/15	60.0
D 5	3.75	21	0	32,000	13	11/15	5/15	47.2
D 22	5.0	24	3	32,000	20	14/15	5/15	61.8
D 23	5.0	24	12	32,000	8	12/15	3/15	67.5
D 17	5.0	25	6	32,000	7	14/15	4/15	69.1
mean	5.0	24	25	32,000	12	40/45	12/45	65.1
D 4	3.75	24	40	33,000	11	11/15	2/15	70.8
D 8	5.0	21	43	33,000	7	10/15	1/15	75.8
mean	3.75-5	23	21	33,000	9	21/30	3/30	72.6
D 13	10.0	5	0	34,000	9	14/15	7/15	48.3
D 9	5.0	6	6	34,000	5	12/15	8/15	30.0
D 3	3.75	6	32	34,000	8	8/15	4/15	38.3
D 10	5.0	16	20	34,000	6	12/15	0/15	90.0
D 6	5.0	20	36	34,000	7	11/15	0/15	86.6
D 14	10.0	24	44	34,000	7	15/15	3/15	80.0
D 15	5.0	24	52	34,000	6	14/15	1/15	89.7
D 16	10.0	25	0	34,000	4	15/15	0/15	100.0
D 18	10.0	25	43	34,000	6	14/15	3/15	75.9
D 12	5.0	29	6	34,000	4	15/15	1/15	93.3
mean	5-10	23	46	34,000	6	96/105	8/105	87.7
D 11	5.0	45	23	34,000	4	14/15	6/15	55.2
D 26	5.0	50	17	34,000	8	14/15	4/15	68.1
D 19	5.0	69	51	34,000	6	15/15	13/15	13.3
D 25	5.0	72	23	34,000	10	9/15	5/15	35.5

\*For explanation and calculation of "probable protection factors," see text.

probability one can assume that with prolongation of the exposure up to the moment when the last mouse of the control group was dying, at most no more additional mice of the protected group will have succumbed than in the control. This would mean, in the example mentioned, a total mortality of 15/15 in the control and of 9/15 in the protected group, resulting in a minimum protection of 40 per cent. The mean between the actual protection and the minimum protection can be regarded as the probable protection, called in this paper "probable protection factor," after omitting the percentage sign.

## RESULTS

Table I summarizes the experiments arranged according to altitude and time interval between prophylactic injection of gitalin and decompression. The probable protection procured depends on the final altitude and on the magnitude of the dose of gitalin. Optimal protection for each altitude is secured by doses of 5 to 10 gamma per Gm. for a period from sixteen until thirty hours after prophylaxis (compare figures in Table I). If one calculates the average probable protection factor for all experiments in which the animals were exposed to the same altitude and treated at the proper time with a sufficient dose, it becomes obvious that the protection factor increases linearly with the altitude (Fig. 1 A). The protection at 34,000 feet is 180.8 per cent of that at 30,000 feet. On account of this strict relation between altitude and protection factor, it is possible, despite the limited number of experiments, to find out the relation between magnitude of dose and protec-

TABLE II  
GITALIN PROPHYLAXIS AGAINST LETHAL EFFECT OF HIGH ALTITUDE.  
INFLUENCE OF MAGNITUDE OF DOSE UPON PROBABLE PROTECTION FACTOR  
(INJECTIONS 16 TO 30 HOURS BEFORE EXPOSURE)

EXP. NO.	DOSE GAMMA PER GRAM	EXPOSURE		DEATH RATIO		PROBABLE PROTECTION FACTOR*	PROBABLE PROTECT. FACTOR CORRECTED FOR 34,000 FT.*
		FEET	TIME MIN.	CONTROL	PROTECT.		
D 1	2.5	30,000	25	6/15	2/15	23.3	42.1
D 5	3.75	32,000	13	11/15	5/15	47.2	60.7
D 4	3.75	33,000	11	11/15	2/15	70.8	79.8
mean	3.75	32,500		22/30	7/30	59.1	71.2
D 20	5.0	30,000	17	11/15	3/15	56.3	100.0
D 24	5.0	30,000	30	11/15	6/15	43.9	79.5
D 22	5.0	32,000	20	14/15	5/15	61.8	79.6
D 23	5.0	32,000	8	12/15	3/15	67.5	87.0
D 8	5.0	33,000	7	10/15	1/15	75.0	85.5
D 6	5.0	34,000	7	11/15	0/15	86.6	86.6
D 10	5.0	34,000	6	12/15	0/15	90.0	90.0
D 12	5.0	34,000	4	15/15	1/15	93.3	93.3
D 15	5.0	34,000	6	14/15	1/15	89.7	89.7
mean	5.0	32,550		108/135	23/135	73.1	87.9
D 21	10.0	30,000	62	4/15	1/15	47.5	85.9
D 14	10.0	34,000	7	15/15	3/15	80.0	80.0
D 16	10.0	34,000	4	15/15	0/15	100.0	100.0
D 18	10.0	34,000	6	14/15	3/15	75.9	75.9
mean	10.0	33,000		48/60	7/60	76.7	85.3

\*For explanation and calculation of "probable protection factors" and their correction for other altitudes, see text and legend for Fig. 1.



tion. All experiments in which the prophylactic injections were given sixteen to thirty hours in advance are summarized and arranged according to the magnitude of the dose in Table II, and their probable protection factors, if necessary, corrected for an altitude of 34,000 feet. Maximal protection is reached, probably in an S-shaped curve, at 5 grains, and doubling this dose does not alter the protection significantly (Fig. 1 B). No attempt was made to use doses above 10 grains, because in preliminary experiments for the determination of the L. D.<sub>50</sub> a dose of 15 gamma occasionally had lethal effects. The time course of the prophylactic effect of a single but optimal gitalin injection (5 to 10 gamma per Gm.) is demonstrated by Fig. 1 C, in which the protection factors (corrected for 34,000 feet, if necessary) are plotted against the time elapsed between injection and altitude exposure.

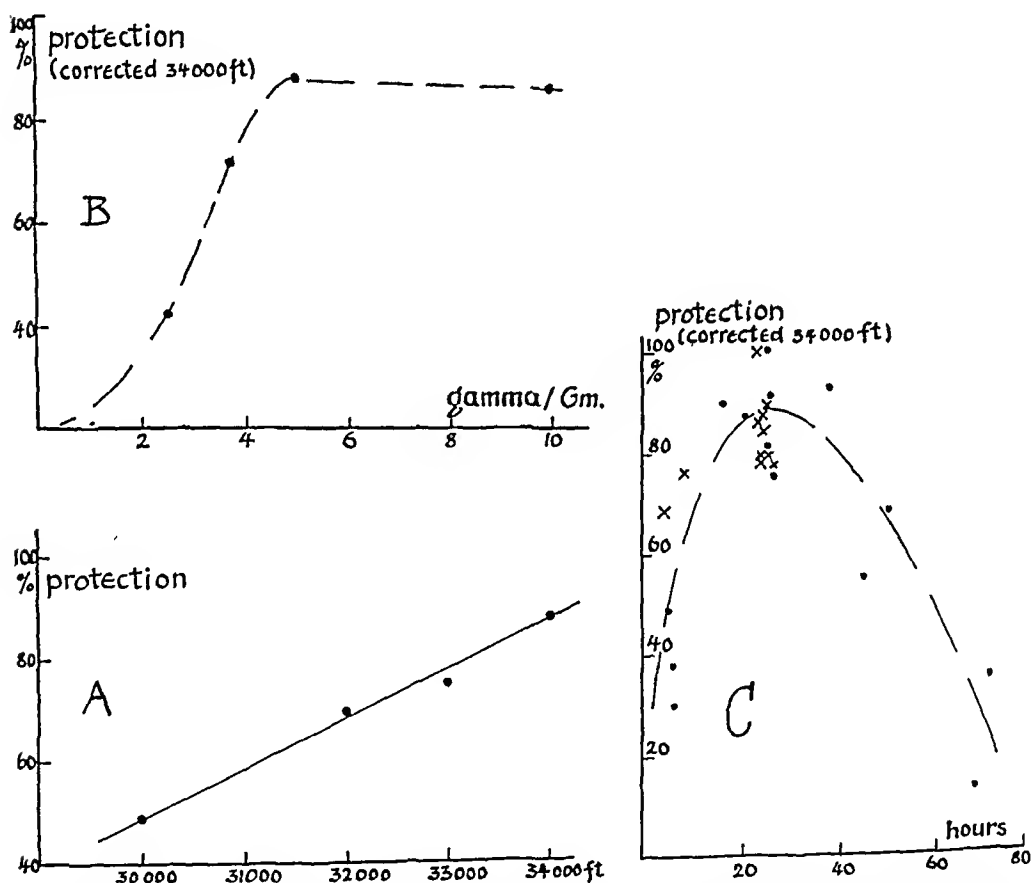


Fig. 1.—A, Average probable protection produced by intraperitoneal injection into mice of 5 to 10 gamma per Gm. of gitalin sixteen to thirty hours previous to exposure to low barometric pressure corresponding to various altitudes. B, Average probable protection produced by giving various doses of gitalin sixteen to thirty hours in advance. Before calculating the average protection, the protection factor for experiments not conducted at 34,000 feet was corrected for that altitude according to the linear relation in A. C, Time course of the probable protection afforded by 5 to 10 gamma per Gm. of gitalin. Black dots represent experiments conducted at 34,000 feet. X, experiments at lower altitude, but protection factor corrected for 34,000 feet.

#### DISCUSSION

The experiments reported here demonstrate clearly the prophylactic value of gitalin against exposure to a high altitude, but do not indicate

in any way by what mechanism this protection is brought about. In normal subjects during severe exercise, Grosemuth and Bansi,<sup>1</sup> as well as Parade,<sup>2</sup> observed an increase in efficiency after nontoxic doses of digitalis. The latter investigator explains these results by the experimentally proved fact that digitalis diminishes the alkali reserve loss which occurs normally during physical exercise. A similar mechanism could be assumed for the high altitude prophylaxis. However, experiments in which it was attempted to influence by various means (e.g.,  $\text{NH}_4\text{Cl}$ ,  $\text{NaHCO}_3$ ) the normal shift in alkali reserve during exposure to high altitude have thus far failed to demonstrate any protective effects. On the contrary, the susceptibility to high altitude was distinctly increased by interference in any direction with the alkali reserve. Another possible mechanism of the gitalin prophylaxis described here might be diminution of the anoxic dilatation of the heart, as reported by Van Lier and co-workers.<sup>3</sup> Probably the gitalin effect results in an improvement of cardiovascular function. Armstrong<sup>4</sup> found in his own experimental work on rats that, at high altitudes (25,000 feet), death was usually caused by depression of the respiratory center, not by circulatory failure. In my experiments on mice, however, there were some indications that, especially at higher altitudes, the circulation stops at a time when the respiratory center is still active. My observations, made by mere inspection, revealed that in those experiments in which death occurred after a few minutes, acute circulatory failure was the main cause of death, whereas in those experiments in which death occurred only after a longer exposure, respiratory failure was responsible for death. This difference in the mechanism of death is probably responsible for the increased gitalin protection at higher altitude, for with increased altitude death occurs more quickly.

Macht,<sup>5</sup> as well as Lehman and Hanzlik,<sup>6</sup> have reported that high altitude (about 10,000 feet) distinctly increases the susceptibility of cats and pigeons to digitalis. Since their experiments dealt only with the emetic and fatal doses of digitalis, they do not have much in common with the experiments reported here. The fact that increasing the dose from 5 to 10 gamma does not improve the prophylactic effect might indicate some harmful influence of the larger dose, although the latter is only one-third of L. D.<sub>50</sub> at sea level.

#### SUMMARY

Gitalin, when given to mice in doses of 5 to 10 gamma per Gm. intraperitoneally, has a high prophylactic effect against the severe, acute anoxemia produced by low atmospheric pressures corresponding to altitudes of 30,000 to 34,000 feet. The protection is at its height for a period of sixteen to thirty hours after injection. The protection afforded increases with the altitude, and reaches nearly 90 per cent at 34,000 feet.

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# LOW VOLTAGE OF THE QRS WAVES IN THE ELECTROCARDIOGRAM, WITH ESPECIAL REFERENCE TO LEAD IV

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THE present study was begun in an attempt to establish the significance of low voltage of the QRS complex in the precordial lead of the electrocardiogram in the presence of normal voltage in the standard leads. Three groups of 100 cases each were analyzed for comparison. Group 1 comprised cases with low voltage in the three classical leads but not in Lead IV (Fig. 1). Group 2 showed normal QRS voltage in the classical leads and low voltage in the fourth lead alone (Fig. 2). Group 3 had low voltage of QRS in all four leads (Figs. 3 and 4). Low voltage was considered to be present in the limb leads if the QRS complexes showed maximal deflections in either direction from the base line of not more than 5 mm. in any of the three leads. In the precordial lead a maximal deflection of 5 mm. or less of the QRS complex in either direction was likewise considered to be low voltage. These measurements were made from the top of the base line to the peak of the R wave, or from the bottom of the base line to the lowest point of the S wave if the downward deflection was the greater in amplitude. In collecting the cases no attempt was made toward selection, and none was eliminated

TABLE I  
GENERAL DATA OF WHOLE SERIES

LOW VOLT- AGE QRS (100 CASES)	AVER- AGE AGE	SEX		BODY BUILD			HEART DISEASE		CONGES- TIVE FAILURE		ECG OTHER THAN VOLTAGE	
		M	F	THIN	OBES.	AVER- AGE	+	0	+	0	NOR- MAL	AB- NOR- MAL
Group 1 (100) Leads I, II, III	55	68	32	20	27	44	65	35	31	69	25	75
Group 2 (100) Lead IV only	51	21	79	11	47	39	47	53	9	91	42	58
Group 3 (100) Leads I, II, III, IV	55	33	67	24	35	41	63	37	26	74	20	80

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from the series because of associated electrocardiographic abnormalities, except that inaccurately standardized tracings were not used. In general, the patients were representative of the cases studied routinely in the cardiac laboratory of the Massachusetts General Hospital during the course of three years (1936-1939), having been referred from both private services and public wards as well as from the outpatient department.

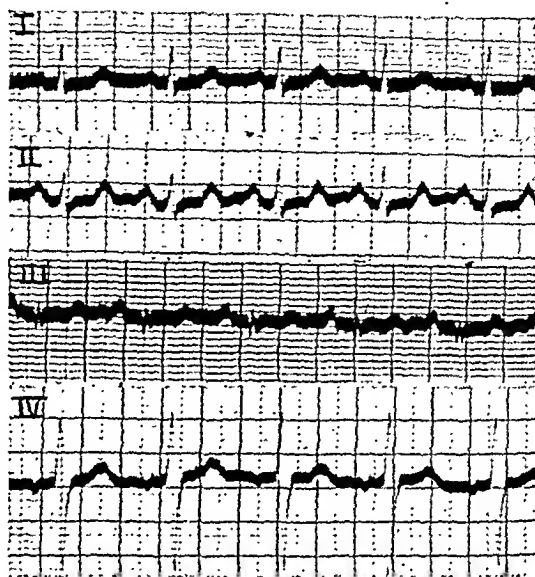


Fig. 1.—Electrocardiograms of male, aged 65 years, of average build. Coronary heart disease with mild angina pectoris. Low QRS voltage in the classical leads but not in Lead IV.

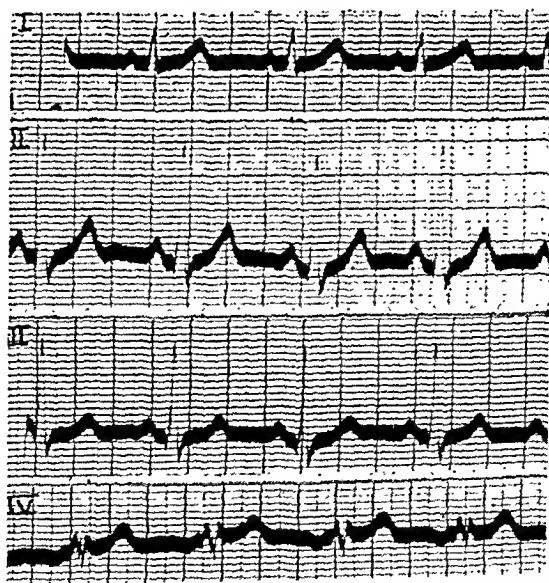


Fig. 2.—Electrocardiograms of thin female, aged 47 years. No heart disease; menopause syndrome. Normal QRS voltage in the classical leads and low in Lead IV.

Striking differences were found in the results derived from the three groups (Table I). The sex ratio was essentially reversed in Groups 2 and 3 as compared with Group 1. Women greatly outnumbered men

in the groups with low voltage of QRS in Lead IV, and men predominated to about the same degree in the group with normal QRS voltage in Lead IV. There were also greater numbers of obese patients in Groups 2 and 3, especially in Group 2, than in Group 1. Heart disease, heart failure, and electrocardiographic abnormalities (including

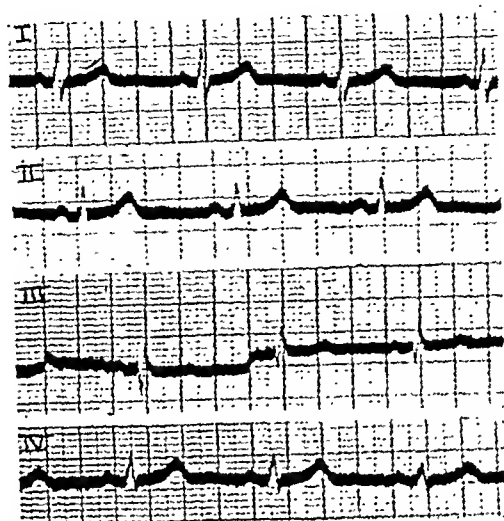


Fig. 3.—Electrocardiograms of obese female, aged 47 years. No apparent heart disease. Poor posture. Low QRS voltage in all four leads.

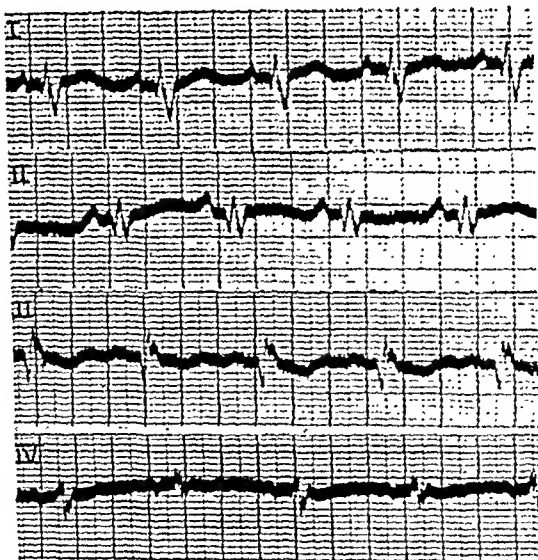


Fig. 4.—Electrocardiograms of moderately obese female, aged 66 years. Coronary heart disease with old myocardial infarction, mild cardiac failure, and pulmonary infarcts. Low QRS voltage in all four leads and bundle branch block.

changes other than T-wave inversion in Lead III and premature beats) predominated to approximately the same degree in Groups 1 and 3. In Group 2, however, the majority of subjects did not have heart disease or associated electrocardiographic abnormalities, and the incidence of heart failure in these persons was practically nil. The quality of the heart sounds roughly paralleled the incidence of heart failure, as did in-

crease in heart size, but these differences between the various groups were not striking and the blood pressure level seemed to be of little or no significance.

TABLE II  
ETIOLOGY IN MODERATE AND SEVERE CARDIAC CONDITIONS

LOW QRS	CORONARY-HYPER-TENSIVE	CORONARY ALONE	CORONARY OCCLUSION, WHOLE GROUP	HYPER-TENSIVE ALONE	RHEUMATIC	MISCELLANEOUS*
Group 1 (57), Leads I, II, III alone	12 (21%)	31 (54%)	25 (44%)	0	6 (11%)	8 (14%)
Group 2 (36), Lead IV alone	18 (50%)	6 (17%)	3 (8%)	5 (14%)	4 (11%)	3 (8%)
Group 3 (58), Leads I, II, III, IV	15 (26%)	29 (50%)	21 (36%)	1 (2%)	10 (17%)	3 (5%)

\*Includes syphilitic, cor pulmonale, pericarditis, congenital, thyroid, calcareous aortic stenosis.

We then analyzed the cases from the standpoint of the etiology of the heart disease (Table II). Here again the patients with low voltage in the standard leads alone showed findings roughly parallel with those of the patients who had low voltage in all four leads. When the QRS complexes were low in the chest lead only, hypertension was more often a factor, either with or without coronary disease. The differences of the percentages of this factor were striking, but they can probably be explained by the higher ratio of women and of obesity in Group 2 and by the milder heart disease.

In addition to the variation in the results among the three groups, one other fact immediately attracted our attention, namely, that the entire series showed a lower incidence of heart disease than we had anticipated. A previous report from this laboratory<sup>1</sup> had indicated that low voltage of QRS in the standard leads of the electrocardiogram was, as a rule, a serious prognostic sign except when accompanying temporary toxic states. Of the fifty-seven patients studied at that time, thirty-four had coronary disease, and all of the rest had other types of heart disease, myxedema, or other serious generalized disease. Hepburn and Jamieson<sup>2</sup> and Turner<sup>3</sup> reported similar findings. Although Willius and Killins<sup>4</sup> did not agree, they had eliminated electrocardiograms abnormal for other reasons from their series and thus had eliminated many of the more serious cardiac cases, so that their results were not strictly comparable with ours. The variation of results in our present series from those of previous reports led us to a further search of the literature for an explanation, and we have found many reports since 1922 which, taken together with our present study, tend to clarify the subject.

Cohn and Raisbeck<sup>5, 6</sup> showed that varying the relationship of the leads to the heart changed the electrical axis recorded. Meek and Wilson,<sup>7</sup> using open-chested dogs and varying the position of the heart, likewise produced changes in the recorded

electrical axis. Contrary to current opinion, they found that rotation around an anteroposterior axis was not important, but that rotation around the heart's longitudinal axis gave the picture of preponderance of one or the other ventricle. Otto<sup>8</sup> applied the same reasoning and the same procedure to the problem of low voltage and found that tipping the apex of the heart upward on a transverse axis through the base produced low recorded voltage of both QRS and T waves in the limb leads. Katz and Ackerman<sup>9</sup> confirmed the work of Otto and of Meek and Wilson and showed that the voltage of both ectopic and normal sinus beats was lowered by these procedures. The effect of the position of the body in producing changes in electrical axis and voltage has been demonstrated by Sigler<sup>10</sup> and Stewart and Bailey,<sup>11</sup> especially good illustrations being shown in the latter paper.

Eyster and co-workers,<sup>12</sup> by cutting or removing various tissues adjacent to the heart, showed that the conduction of currents away from the heart was by means of preferential pathways and that the electrical field of the heart approximated a plane. This was confirmed by Katz and Korey,<sup>13</sup> who produced a lowering of the recorded potential in the limb leads by insulating various proximal structures from the heart with rubber sheeting. The large posterior muscle group, the chest wall itself, and the diaphragm were found to be good conductors, while the lungs and great vessels were poor ones. They felt that these findings nullified the principles of the Einthoven triangle, since the recorded axis seems to depend on the parts of the heart in contact with the good conductors rather than the heart's relationship to any particular electrical vector.

Wilson,<sup>14</sup> in discussing the principles of the Einthoven triangle, pointed out on theoretical grounds that an increase in the conductivity of tissues in contact with the heart should also lower the recorded voltage in the limb leads. He considered as the possible responsible factors for low voltage in any given case: (1) lowered potential produced by a diseased condition of the heart muscle; (2) accidental neutralization of effects of different parts of the heart; and (3) changes in conductivity of tissues adjacent to the heart. Katz and his co-workers<sup>15</sup> confirmed this by the introduction of good conductors between the heart and the usual conducting pathways, producing low voltage of the records, presumably by the introduction of shunts or by bringing into contact with the pathways larger areas of the heart muscle and thereby producing neutralizing effects. As suggested by Wilson, pleural effusions, pericardial effusions, adhesions, and pulmonary consolidation or edema would act in a similar manner, probably accounting for some of the discrepancies observed in the axis shifts in cases of pneumothorax and pleural effusion.<sup>16, 17</sup> To obviate the possibility that the open thorax plays a role, Katz and his group repeated their study of the conducting pathways, closing the thorax each time.<sup>18</sup> Their findings were essentially the same this time, except that they used a different method in severing the great vessels and concluded that they actually accounted for a considerable proportion of the conduction of currents.

We found no reported series with standard technique for the application of Lead IV in which the voltage had been specifically studied. However, several authors<sup>19-23</sup> have pointed out that the position of the chest electrode is important with reference to the relative sizes of R and S waves and, to a lesser extent, to the maximum potential recorded. Hoffman and Delong<sup>19</sup> stated that the voltage was usually greater when the anterior electrode was close to the apex of the heart and also that the voltage of the chest lead was not necessarily parallel to that of the limb leads. Katz and Kissin<sup>24</sup> felt that low voltage was due to: (1) intraventricular block, (2) a relative shunt of currents away from the electrodes, or (3) a change in the position of the heart, making the long axis more perpendicular to the plane of the leads. They suggested that discrepancies between the voltage in limb leads and in the chest lead might differentiate "shunts" from changes in the position of the heart. Goldbloom<sup>25</sup> found low voltage in the chest lead only in cases of coronary



disease, but his normal series (twenty-five cases) was small, and Master<sup>20</sup> in 104 normal adults noted low voltage of the chest lead sometimes when the anterior electrode was placed outside of the cardiac apex. Roth's illustrations<sup>21</sup> were interesting because they showed variations in the voltage of the QRS complexes on shifting the indifferent as well as the chest electrode. The effects of shifting the position of the chest electrode were studied specifically by Edwards and Vander-Veer,<sup>22</sup> who confirmed the impressions of the others that the main changes were in the relative sizes of the R and S waves, but their tracings also showed variations in the maximum potential.

Using these data from the literature we separated our cases into cardiac and noncardiac groups and attempted to evaluate them on the basis of the presence or absence of probable explanations for the occurrence of low voltage (Table III). In the category of extracardiac disease, we included conditions which we felt should affect the body as a whole, such as severe infections, anemia, malnutrition, hypothyroidism, uremia, etc., and those which would change the conductivity of tissues in the chest, such as pulmonary fibrosis, consolidation, effusions, pulmonary edema, etc. We then considered as other probable factors conditions which would alter the position of the heart, such as abnormal body builds, emphysema, spinal deformities, abdominal disease elevating the diaphragm, etc. In the cases of low voltage in Lead IV we considered the female sex and obesity as probable factors because of the likelihood of errors in placement of the chest electrode. It seemed wise to compare the results in the noncardiac subjects with those in moderate and severe cardiac patients only, leaving out cardiac patients who were asymptomatic and without enlargement, since it was unlikely that such a mild degree of heart disease in itself could play a role in the production of low voltage.

The results of this analysis, shown in Table III, were instructive in several points. In all three groups there was more extracardiac disease in the cardiac cases than in the noncardiac cases, mainly because of the inclusion of the signs of heart failure, but this finding was considerably less frequent in Group 2 than in the others. Factors such as abnormal body build, etc., were about equally divided in all three groups between the cardiac and noncardiac subjects, but Group 2 contained a much greater percentage of these cases. Of the twenty-four cardiac patients who had no failure, other disease, or other apparent factors, seventeen had had coronary thrombosis, three had bundle branch block, and two each had marked left axis deviation and pericarditis—in other words, evidence of considerable heart disease. We were then left with thirty persons who were apparently entirely healthy physically and who had no evident explanation of any sort for the presence of low voltage in the electrocardiograms, an incidence of 10 per cent of the whole series. Of these, eighteen (6 per cent) showed low voltage in the classical leads and seven (2 per cent) in all four leads. These percentages are considerably higher than those reported by Shipley and Halloran<sup>27</sup> and Chamberlain and Hay<sup>28</sup> in normal subjects.

TABLE III  
COMPARISON OF FACTORS OTHER THAN HEART DISEASE

LOW VOLTAGE QRS (300 CASES)	EXTRACARDIAC DISEASE IN			OTHER PROBABLE FACTORS IN				NO APPARENT EXTRACARDIAC FACTORS IN		
	MODERATE AND SEVERE CARDIAC PATIENTS	NON- CARDIAC PATIENTS	MILD CARDIAC PATIENTS	MODERATE AND SEVERE CARDIAC PATIENTS	NON- CARDIAC PATIENTS	MILD CARDIAC PATIENTS	MODERATE AND SEVERE CARDIAC PATIENTS	NON- CARDIAC PATIENTS	MILD CARDIAC PATIENTS	
Group 1 (100), Leads I, II, III only	36 (63%)	13 (37%)	3 (38%)	7 (12%)	4 (11%)	1 (13%)	14 (24%)	18 (51%)	4 (50%)	
Group 2 (100), Lead IV only	15 (42%)	17 (32%)	2 (18%)	18 (50%)	31 (58%)	8 (73%)	3 ( 8%)	5 ( 9%)	1 ( 9%)	
Group 3 (100), Leads I, II, III, IV	41 (71%)	21 (57%)	3 (60%)	10 (17%)	9 (24%)	1 (20%)	7 (12%)	7 (19%)	1 (20%)	

McFarland and his associates,<sup>29</sup> however, have studied 173 normal healthy aviators and found low voltage of the QRS complexes in the classical leads alone in 8 per cent, in Lead IV alone in 5 per cent, and in all four leads in one case (0.6 per cent). Furthermore, 30 per cent of their entire series showed voltage in the classical leads of less than 0.8 mv. All of these electrocardiograms were normal in other respects, and there was no obvious explanation for the occurrence of low voltage in any of these cases.

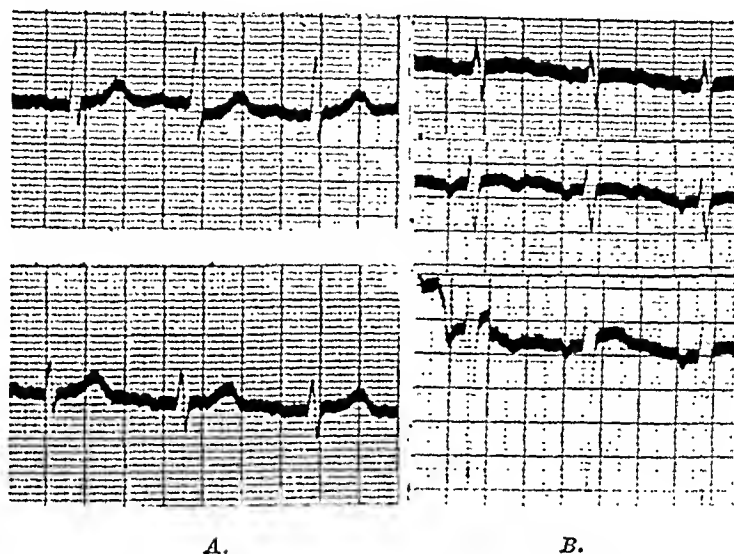


Fig. 5.—Chest leads in different patients. A, Both tracings were taken at the apex of the heart in an obese woman, showing the effect of breast tissue on the voltage of the chest lead. The upper record was taken with the precordial electrode placed at the cardiac apex and *underneath* the thick, pendulous breast; the lower record, with the electrode at the cardiac apex but *overlying* the breast. B, Electrocardiograms of woman of average build, with firm breast. Low voltage in both strips at the apex, with the electrode, first, so far as possible underneath the breast and, second, overlying the breast, but normal voltage in the lowest strip at the left sternal border.

During the analysis of our series we were impressed by the fact that the voltage was extremely variable in many of the cases without any comparable changes in the condition of the patients. This was especially true in Lead IV, and it seemed likely that variation in placing the chest electrode was a factor of significance. Twenty patients were studied with this in mind, and it was found, as other authors had already noted, that the voltage changed as the electrode was moved to various other positions on the chest. Furthermore, the voltage fluctuated with different phases of respiration in some patients, and in others, placing the electrode under the breast at the apex of the heart resulted in a normal recorded voltage when the voltage had been low with the electrode over the breast at the apex. Apparently the amount of tissue between the heart and the electrode was as important as the position of the electrode with reference to the frontal plane of the heart (Fig. 5). In male patients it followed that a thick chest wall or obesity might account for low voltage in Lead IV in a similar manner as in females, and although we had no way of adequately testing this theory, it was observed in a few cases that loss of a pathologic amount of excess weight was followed

by a return of the voltage to normal in the chest lead, and in at least one patient loss of weight resulted in a return to normal of low voltage in the classical leads (Fig. 6).

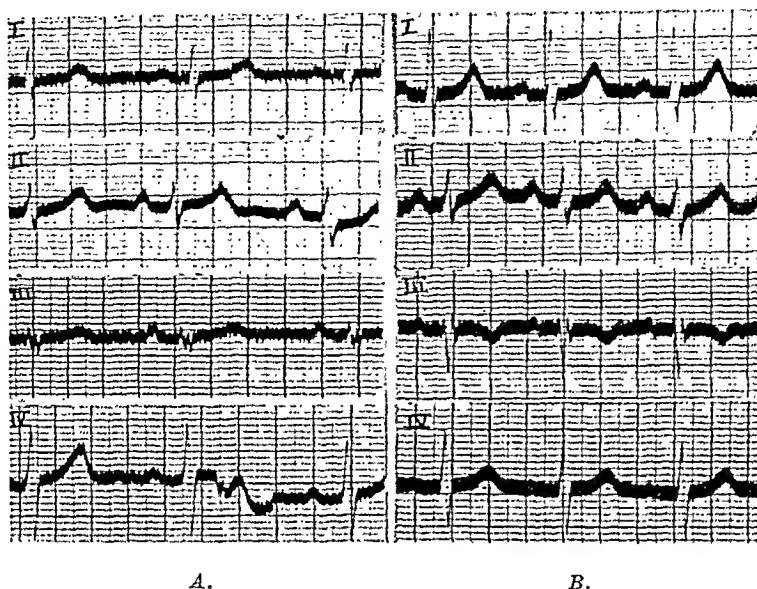


Fig. 6.—Electrocardiograms of obese female, aged 17 years. No apparent heart disease, but possibly rheumatic fever. A, At 160 pounds; B, at 143 pounds.

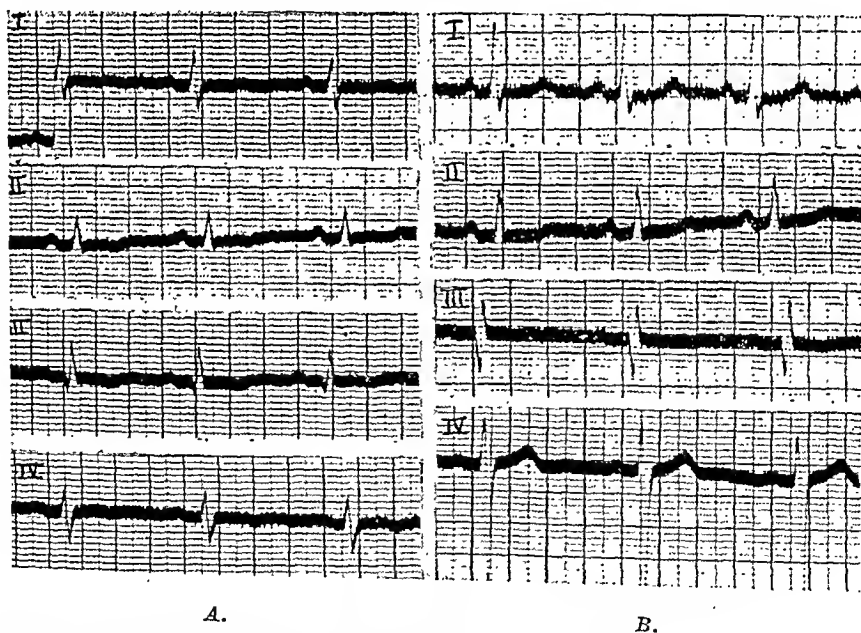


Fig. 7.—Four lead electrocardiograms before (A) and after (B) treatment of myxedema with thyroid extract. The patient was a slightly obese female, aged 58 years, with no evident heart disease.

In clear-cut myxedema, the QRS voltage tends to be distinctly low in all four leads and is amplified to the usual normal range by thyroid therapy (Fig. 7).

After obtaining the data from our complete series of 300 cases, we wondered whether different figures might be obtained from cases of



accompanying electrocardiographic abnormalities, especially in the shape and direction of the QRS waves and the shape and direction of the T waves. It is true, however, that more than one-half of all our patients with low QRS voltage, less commonly in Group 2, had such other electrocardiographic abnormalities, and the presence of low voltage paralleled the appearance of congestive failure. To that extent, the low QRS voltage is significant in relation to heart disease. The important point from this analysis is that low QRS voltage alone is not indicative of heart disease or, necessarily, of any other trouble, as Willius pointed out years ago, but is apparently dependent on variations in the relationship of the position of the heart to the leads themselves or to the manner in which the currents are conducted away from the heart.

#### SUMMARY

Analysis was made of 300 cases showing low voltage of the QRS complexes of the electrocardiogram. Three groups of 100 cases each were compared with one another; Group 1 having low voltage of QRS in the classical leads but normal voltage in the precordial (fourth) lead, Group 2 having low voltage of QRS in the fourth lead alone, and Group 3 having low QRS complexes in all four leads.

Evidence of heart disease was found in only 57 per cent of the entire series, and only 47 per cent of the group with low voltage in the chest lead alone had evidence of heart disease.

Generalized debilitating diseases, changes in the position of the heart, and changes in the conductivity of adjacent tissues seemed to be important factors in the production of low voltage of the QRS complexes. Furthermore, the thickness of the chest wall and the position of the precordial electrode influenced the voltage of QRS in Lead IV.

Heart disease was of no greater relative importance than extracardiac factors in cases showing extreme reduction in QRS voltage (for instance, 0.3 mv. or less). However, in such cases the responsible factor was likely to be more obvious than in cases with moderate degrees of low voltage.

Analysis of the literature likewise indicates the importance of the factors mentioned above.

Even in the patients with considerable heart disease, fluctuations in the voltage, with changes in the state of compensation, suggested that the heart lesions were of less importance than the secondary manifestations of heart failure in the production of lowered potential.

Ten per cent of the entire series showed no evident explanation of any sort for the occurrence of low voltage, being apparently healthy normal persons in every respect.

Our study indicates that the solitary finding of low voltage of the QRS complexes is of little or no diagnostic value regarding the presence or absence of heart disease or of any other trouble. The wider use of

electrocardiograms on normal people outside of hospitals will probably show a higher incidence of low voltage than the literature suggests at present.

We are indebted to Dr. Sherman Golden for help in the collection of cases at the beginning of this study.

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brought by the increased flow of blood and thus some of the benefits are neutralized.<sup>4</sup>

The principle of reflex vasodilatation, that is, the induction of vasodilatation by applying heat to an extremity other than the one being studied, has been known since Sewell and Sanford<sup>5</sup> observed in 1890 that immersion of one hand in hot water (48° C.) increased the volume flow of blood in the opposite extremity. Winkler<sup>6</sup> in 1902 observed flushing of rabbits' ears when the hindquarters were immersed in hot water. Stewart,<sup>7</sup> in 1911, decided that immersion of one arm in hot water increased blood flow in the opposite extremity, for the loss of heat, measured calorimetrically, was increased from the extremity opposite to the immersed one. In 1931, Lewis and Pickering<sup>8</sup> found that the temperature of the skin of the digits of human subjects could be increased by warming the body which was enclosed in a heating cabinet from which the extremities protruded. Gibbon and Landis<sup>9</sup> and Landis and Gibbon<sup>10</sup> showed that an increase in temperature of the skin of the toes could be produced by immersing the forearms in warm water. Similar observations were made by Grant and Holling,<sup>11</sup> Freeman,<sup>4</sup> and Wright and Phelps.<sup>12</sup> Pickering,<sup>13</sup> Pickering and Hess,<sup>14</sup> and Landis and Gibbon<sup>10</sup> have shown that reflex vasodilatation depends on venous blood returning from the warmed extremity (afferent limb of the reflex arc) and on the sympathetic nervous system (efferent limb of the reflex arc). These observations have been confirmed by Fatherree and Allen.<sup>15</sup>

#### THE HEATING UNIT

To apply the principle of reflex vasodilatation we suggested a heating unit which was constructed for us by the Colvinex Corporation through the kindness of Mr. Paul Gaynes, the president. The apparatus consists of a fine copper wire woven by a special process onto a fireproof cloth. This is incorporated into a waterproof and washable cover. A transformer reduces the voltage to 10; a fuse protects against short circuits, and a thermostat included in the units prevents the temperature from increasing to more than 43° C. Although these units probably can be improved further in some details, the principle of their use seems established. We have tentatively designated the units as "heating sleeve" and "heating boot" as applied to the upper and lower extremities, respectively.

#### PLAN OF STUDY

Twelve normal individuals and thirteen patients with hypertension were studied under controlled conditions. Tobacco and food were withheld for twelve hours preceding the study. The subjects were placed at rest in the supine position in a room in which the temperature was maintained about 22° C. Changes of position and psychic disturbances were eliminated as much as possible to avoid extraneous influences.<sup>16-18</sup>

The temperature of the skin of the fingers and toes was measured by the Sheard electromotive thermometer.<sup>19</sup> The circulation was considered to be in a basal state when the temperature of the skin remained at a fairly constant level. Usually an hour was required for this stabilization.

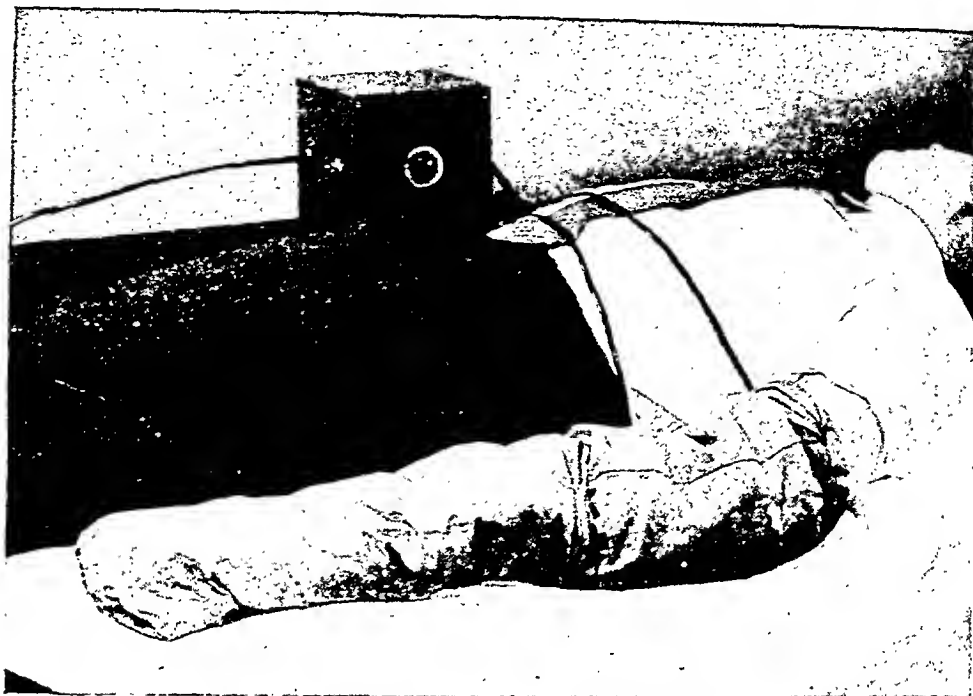


Fig. 1.—The heating sleeve applied to the arm. A heating boot can be applied to the leg in a similar manner.

The blood flow in an arm of each of nine of the twelve normal individuals and of ten of the thirteen patients with hypertension was measured with the plethysmograph. The blood flow was determined for the basal state. Then the preheated heating sleeve was applied to the upper extremity which was not in the plethysmograph (Fig. 1).<sup>\*</sup> The temperature of the skin of the other three extremities including the one in the plethysmograph was recorded every ten minutes. Determinations of blood flow were made with the plethysmograph at various stages of vasodilatation. When the temperature of the skin reached a maximal level, the blood flow then determined was designated "the blood flow of maximal skin temperature."

The term "vasodilatation" is used throughout this paper because of common usage, although "arteriolar dilatation" would be better because it designates the mechanism by which the volume flow of blood is increased.

#### RESULTS

*Skin Temperatures.*—The temperature of the skin of the toes of all but two of the normal subjects and of all but one of the patients with hypertension increased in response to the application of the heating

<sup>\*</sup>Some of our patients have used the units continuously for several days without harm. A mild erythema, which disappeared promptly, has been noted, however.

sleeve to a forearm and hand. All individuals studied had an increase in the temperature of the skin of the fingers of the opposite hand. The response in one case is shown in Fig. 2. A high level of vasodilatation which we believe is indicated by the high level of skin temperature was produced and maintained as long as the heating sleeve was applied. On removal of the unit, the fingers and toes quickly cooled.

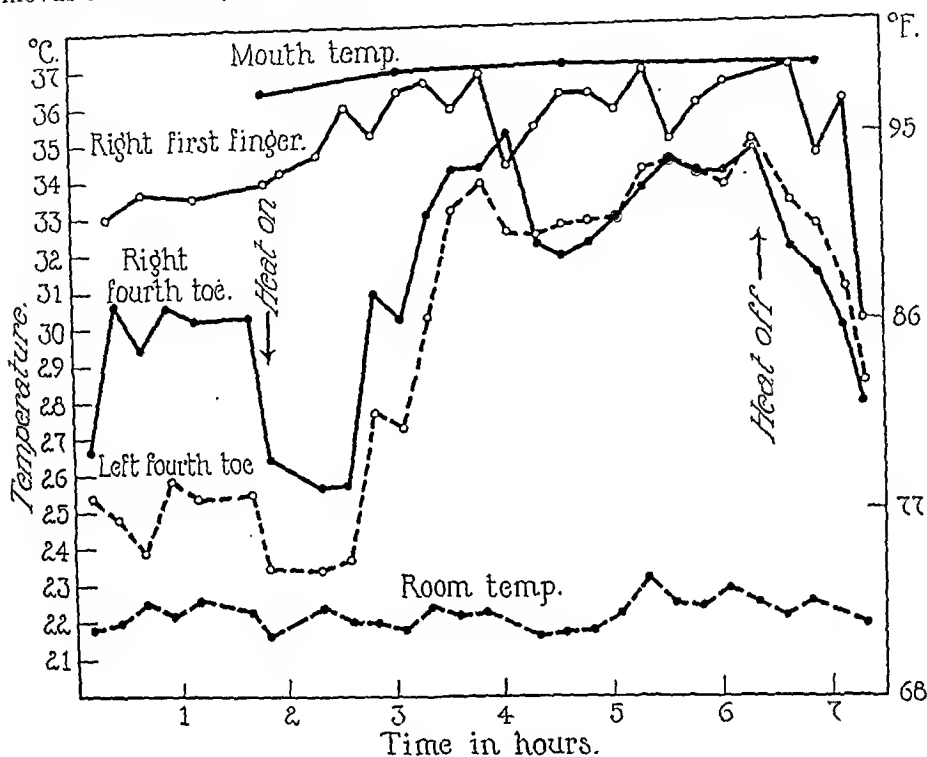


Fig. 2.—Effect on temperature of skin of toes and of the right first finger of the application of the heating sleeve to the left arm. The temperature of the skin of the right first finger increased  $2.1^{\circ}\text{C}$ . and that of the right and left fourth toes,  $9.4^{\circ}$  and  $11.5^{\circ}\text{C}$ . respectively (Table I, Case 1).

Failures of vasodilatation such as occurred in three of our cases have been noted when other methods have been used.<sup>8, 9</sup> Failure seems related to inadequate heat which is applied to inadequate body surface. The three cases in which vasodilatation did not occur in the toes were excluded from further consideration in the study on temperatures of the skin.

For the normal individuals the mean basal temperature of the right fourth toe was  $27^{\circ}\text{C}$ . and the mean basal temperature of the left fourth toe was  $26.5^{\circ}\text{C}$ . The mean maximal temperatures of the respective toes were  $33.9^{\circ}\text{C}$ . and  $33.6^{\circ}\text{C}$ . The mean basal temperature of the fourth finger on the left hand was  $30.6^{\circ}\text{C}$ . and the mean of the highest reading was  $35.5^{\circ}\text{C}$ . (Table I). The mean increase in the temperature of the skin of the respective toes was  $6.9^{\circ}\text{C}$ . and  $7.0^{\circ}\text{C}$ . and the mean increase in the temperature of the skin of the fingers was  $4.9^{\circ}\text{C}$ .

In the group of patients with hypertension, the mean basal temperature of the right fourth toe was  $28.4^{\circ}\text{C}$ . and of the left fourth toe  $28.3^{\circ}\text{C}$ .

C. The mean maximal temperatures were 34.6° and 33.8° C., respectively. The mean basal and maximal temperatures of the skin of the fourth finger on the left hand were 32.6° and 35.9° C., respectively (Table II).

TABLE I

EFFECT OF APPLYING A HEATING SLEEVE TO THE RIGHT UPPER EXTREMITY ON THE TEMPERATURE OF THE SKIN OF THE DIGITIS OF NORMAL SUBJECTS

CASE	TEMPERATURE OF SKIN IN DEGREES C					
	FOURTH TOES				FOURTH LEFT FINGER	
	RIGHT		LEFT			
	BASAL	MAXIMAL	BASAL	MAXIMAL	BASAL	MAXIMAL
1*	25.6	35.0	23.2	34.7	34.5†	36.6†
2	21.5	35.4	20.7	34.9	25.6	36.2
3	23.6	32.9	23.0	33.0	28.6	35.8
4	25.3	34.5	28.7	35.2	31.6	36.0
5	27.9	34.0	28.6	33.8	33.0	35.3
6	30.6	33.9	30.6	33.6	33.5	35.6
7	32.8	35.0	32.9	34.6	28.8	34.8
8	29.5	34.4	25.1	30.2	31.0	35.2
9	21.6	31.0	21.3	32.4	27.1	36.8
10‡	31.4	32.7	31.2	33.5	32.0	32.5
Range	21.5- 32.8	31.0- 35.4	20.7- 32.9	30.2- 35.2	25.6- 34.5	32.5- 36.8
Mean	27.0	33.9	26.5	33.6	30.6	35.5

\*Heating sleeve was on left upper extremity.

†Temperatures from right first finger.

‡In cases 11 and 12 the temperature of the skin of the toes did not increase.

TABLE II

EFFECT OF APPLYING A HEATING SLEEVE TO THE RIGHT UPPER EXTREMITY ON THE TEMPERATURE OF THE SKIN OF THE DIGITS OF PATIENTS WITH HYPERTENSION

CASE	TEMPERATURE OF SKIN IN DEGREES C					
	FOURTH TOES				FOURTH LEFT FINGER	
	RIGHT		LEFT			
	BASAL	MAXIMAL	BASAL	MAXIMAL	BASAL	MAXIMAL
13	25.3	34.6	25.8	34.2	35.6	36.8
14	33.4	34.0	33.2	34.9	36.1	36.2
15	24.0	31.0	24.5	32.4	32.0	36.0
16	27.0	33.5	26.0	33.5	29.0	35.8
17	22.0	33.0	22.0	33.1	32.0	36.3
18	28.6	36.5	28.0	36.0	31.0	36.8
19	24.1	36.4	24.0	26.3	31.0	35.8
20	31.9	34.8	32.8	32.8	34.0	34.7
21	33.0	34.9	33.1	35.2	34.1	35.8
22	26.5	35.0	25.5	34.4	31.9	35.4
23	33.5	35.8	33.6	36.0	32.0	35.6
24*	31.3	35.9	30.6	36.4	34.5	36.0
Range	22.0- 33.5	31.0- 36.5	22.0- 33.6	26.3- 36.4	29.0- 36.1	34.7- 36.8
Mean	28.4	34.6	28.3	33.8	32.6	35.9

\*In Case 25 the temperature of the skin of the toes did not increase.

The mean increase in the temperature of the skin of the respective toes was 6.2° and 5.5° C., and in the temperature of the skin of the fingers, 3.3° C.

*Blood Flow.*—The blood flow of all of the nineteen subjects studied increased in the arm opposite the one heated. The response of one individual is shown in Fig. 3. The blood flow increased from a basal

TABLE III

THE EFFECT OF APPLYING A HEATING SLEEVE TO THE OPPOSITE ARM ON THE VOLUME FLOW OF BLOOD TO AN UPPER EXTREMITY OF NORMAL SUBJECTS.  
DETERMINATIONS MADE WITH A PLETHYSMOGRAPH

CASE	BLOOD FLOW PER MINUTE PER 100 C.C. OF ARM TISSUE				PERCENTAGE INCREASE IN BLOOD FLOW
	BASAL STATE	STATUS OF VASODILATATION (DETERMINED BY SKIN TEMPERATURE)			
		MILD	MODERATE	MAXIMAL	
1	2.10	2.68	3.47	4.68	123
2	2.43	4.18	6.04	7.63	214
3	2.55	4.30	6.93	5.10	100
4	4.94	7.36	12.36	16.08	226
5	1.64	2.22	2.70	2.88	76
6	2.98	4.56	4.33	8.45	184
7	2.42	4.38	5.19	7.39	205
8	1.64	1.60	2.72	2.88	76
11	2.63	4.10	6.03	7.46	184
Range	1.64- 4.94	1.63- 7.36	2.70- 12.36	2.88- 16.08	76- 226
Mean	2.59	3.93	5.53	6.95	168

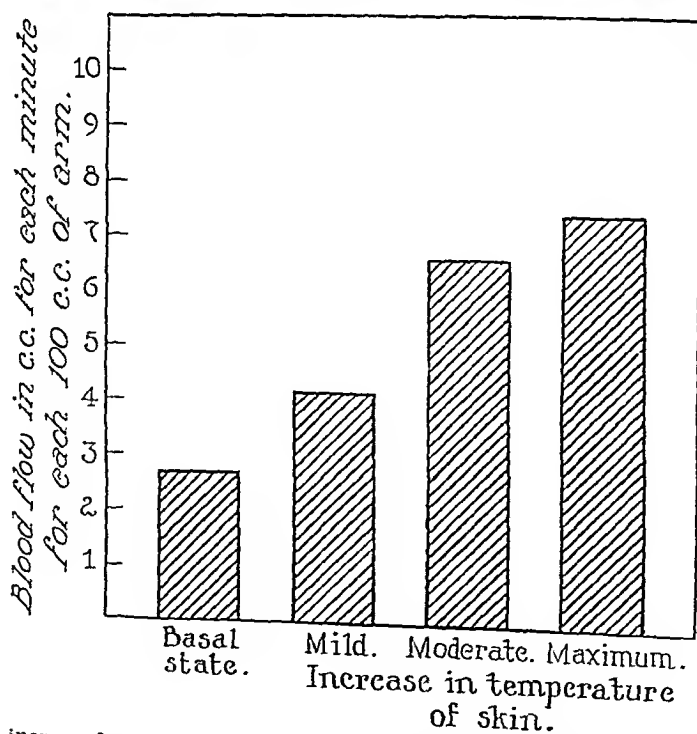


Fig. 3.—The increased volume flow of blood in one arm resulting from application of a heating sleeve to the other arm (Table III, Case 11).

level of 2.63 c.c. per minute per 100 c.c. of arm to 7.56 c.c. per minute per 100 c.c. of arm. This was an increase of 184 per cent. The average blood flow for the nine normal individuals (Table III) was 2.59 c.c. per

minute per 100 c.c. of arm in the basal state. The average blood flow determined when the temperature of the skin was maximal was 6.95 c.c. per minute per 100 c.c. of arm, or an average increase of 168 per cent.

TABLE IV

THE EFFECT OF APPLYING A HEATING SLEEVE TO THE OPPOSITE ARM ON THE VOLUME FLOW OF BLOOD TO THE UPPER EXTREMITY OF PATIENTS WITH HYPERTENSION. DETERMINATIONS MADE WITH THE PLETHYSMOGRAPH

CASE	BLOOD FLOW PER MINUTE PER 100 C.C. OF ARM TISSUE				PERCENTAGE INCREASE IN BLOOD FLOW
	BASAL STATE	STATUS OF VASODILATATION (DETERMINED BY SKIN TEMPERATURE)			
		MILD	MODERATE	MAXIMAL	
15	5.64	6.04	9.16	9.97	77
16	1.65	1.91	3.71	5.16	213
17	1.47	1.90	2.00	1.74	18
18	3.24	3.79	4.53	5.50	70
20	1.92			2.25	17
21	3.80			5.65	49
22	4.05			7.59	87
23	2.93			7.49	156
24	2.53			14.50	473
25	2.55	3.07	4.06	7.72	203
Range	1.47- 5.64	1.90- 6.04	2.00- 9.16	1.74- 14.50	17- 473
Mean	2.98	3.34	4.69	6.76	127

In the series of cases of hypertension similar increases in the blood flow were noted (Table IV). The average blood flow determined in these cases at basal state was 2.98 c.c. per minute per 100 c.c. of arm. The average blood flow determined at maximal skin temperature was 6.76 c.c. per minute per 100 c.c. of arm. There was an average increase in blood flow of 127 per cent in the arm in response to the application of a heating sleeve to the opposite arm.

For four individuals the blood flows of the forearm and hand and then of the forearm alone were determined. The latter calculation was made by occluding the arterial circulation at the wrist. These studies indicate that the percentage increase in circulation to the hand was usually greater than in that to the forearm.

There may have been some inaccuracies in the measurement and calculation of the blood flow with the plethysmograph. Thus figures for blood flow are approximate and not absolute values. Any inaccuracies which may have been present appear to be constant, and the relation of the various figures given for the calculation of blood flow in the same extremity of the same subject is probably accurate. Studies which are incomplete at present indicate that increases in temperature of the skin occur in the presence of chronic occlusive arteriolar diseases when the heating sleeve is used, although the increases are not so great as those of normal individuals. Also, studies indicate that the effects on circulation just reported persist as long as the heating unit is applied.

## PROPOSED CLINICAL USE

At present we can only theorize about the clinical value of these units. Their use, however, might contribute substantially to reduction of the incidence of venous thrombosis, thrombophlebitis and pulmonary embolism following operation. Smith, Craig, and one of us (Allen)<sup>20, 21</sup> have shown that after operation the venous blood flow ordinarily slows up. This factor is probably important in the genesis of the postoperative complications just mentioned. Moreover these observers have shown that when the skin is warm, blood flows rapidly in the veins, and when the skin is cold, blood flows slowly in the veins.<sup>20, 21</sup> Hence use of the heating boot or sleeve after operations should prevent the slowing of the venous circulation which ordinarily occurs and perhaps prevent or diminish the postoperative complications mentioned.

The units might well replace hot, moist packs in some instances such as in the treatment of phlebitis. A unit might be modified for the purpose of keeping moist dressings hot. This would find ready application in the treatment of cellulitis, lymphangitis, phlebitis, and similar conditions. In the treatment of arthritis and painful joints attributable to other causes, these units should be useful for they allow the application of heat continuously for long periods. Dr. C. H. Slocumb, of the Clinic, believes that these units afford the most satisfactory method of applying heat locally to arthritic joints. The physical therapist may find other uses.

The heating sleeve and heating boot should be valuable in increasing the blood flow in limbs in which it is diminished because of chronic arterial occlusion. The blood supply can be increased through collateral arteries which are not occluded. In disorders such as arterial embolism, in which vasospasm plays a major role, an increase in blood supply should be attained by release of this vasospasm.

Theoretically these heating units have advantages which many other methods used to improve the circulation do not have; further clinical experience is necessary before their therapeutic value can be evaluated accurately. Investigations of this nature are in progress and will be reported later.

## SUMMARY AND CONCLUSIONS

The following conclusions can be drawn from our data concerning the response to application of the heating sleeve to an upper extremity.

1. The temperature of the skin of the digits of all the other extremities increases in most instances.
2. The volume flow of blood of the opposite upper extremity increases and probably a similar effect is produced in the lower extremities because the temperature of the skin of the toes usually increases.

Studies on the clinical value of these units are in progress. Several conditions in which they might be used advantageously have been suggested.



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## DISCUSSION

DR. NORMAN E. FREEMAN, Philadelphia.—The observations which we have made, both at Boston and Philadelphia, are entirely in agreement with those that Dr. Allen and Dr. Brown have described. Dr. Landis and Dr. Gibbon, in 1934, described the vasodilatation test in which heat was applied to two of the extremities and the skin temperature was measured in the other two. The procedure which Dr. Allen and Dr. Brown have shown us is essentially the one which we are using today routinely in the Vascular Clinic in order to measure the capacity for vasodilatation.

In the Vascular Clinic of the University of Pennsylvania in the past five years over a thousand vasodilatation tests have been performed on patients with various degrees of arterial occlusion. At first, Dr. Landis thought that this procedure might be therapeutically effective as a means of increasing blood flow after arterial occlusion, just as Dr. Allen has suggested. He did not take up this type of treatment because he found in a large series of cases that the more the arterial obstruction the less vasodilatation was possible.

In observations on the blood flow through the hand, when heat was applied to the body, we found that, when the circulation was badly occluded, as in advanced Buerger's disease, it was impossible to get an increase in the blood flow. When the tissues are in jeopardy so that the local demand for blood cannot be satisfied, I think that there is already a maximum stimulus for arterial inflow, and that reflex vasodilatation will not increase the circulation.

Therefore, when the need is greatest, in pregangrene cases, there is least success with this type of treatment. In the vasospastic group of cases it is very helpful, because a condition of prolonged increase in blood flow can be maintained without harm to the patient and with relatively little expense and trouble. I think that this is a field in which Dr. Allen's therapeutic suggestion will be worth while.

DR. D. I. ABRAMSON, Cincinnati.—I should like to ask Dr. Allen whether he would consider this treatment of use in cases in which there is a decrease in blood supply to the muscle. It would seem that, from most of the evidence presented thus far, the so-called Landis response takes place in the skin vessels and not in the muscle vessels.

DR. EDGAR V. ALLEN, Rochester, Minn.—Dr. Freeman's point is a very good one. This method of treatment will not make blood flow through arteries which are occluded organically. However, it is almost invariably true that, when there is chronic occlusion of the main arteries, there is also further impairment of the circulation as a result of either vasospasm or incomplete vasodilatation. One may almost always improve the circulation by various means in extremities in which blood flow is diminished chiefly because of organic changes. I do not know that our method is any better or any worse than other methods of improving the circulation, but theoretically, at least, it is just as good if it produces increases in the temperature of the skin and in blood flow as other methods of treatment do.

I do not think it has been reliably demonstrated that sympathectomy and fever, for example, increase the blood flow only to the skin and not to the muscle. The studies so far have been based largely upon measurement of the temperature of the muscle, and it has not been shown that this is a reliable method of estimating blood flow in muscle. Be that as it may, in chronic occlusive arterial disease gangrene does not affect the muscle of the calf, for example, but affects the skin of the digits. Hence I think it is of little moment whether or not this method increases the flow of blood to the muscle in the calf of the leg. If one can improve the circulation to the skin of the digits of a patient with chronic occlusive arterial disease, then he has done something which is of value from the standpoint of treatment. It is almost certain that improvement in the circulation to the muscle of distal parts of the extremities is increased likewise.

# THE AURICULOVENTRICULAR RATIO AND ITS RELATIONSHIP TO THE ELECTRICAL AXIS OF THE HEART

A. HENRY CLAGETT, JR., M.D.

PROVIDENCE, R. I.

THE aim of this study was to determine the relationship, if any, between the roentgenologic auriculoventricular (A-V) ratio and the electrical axis of the heart, and, in doing so, to determine the reliability of the A-V index as related to clinical medicine.

In 1898, Rummo,<sup>1</sup> an Italian clinician and anatomist, described, without the aid of the x-ray, a line on the cardiac silhouette corresponding to the auriculoventricular septum. However, he made no mention of an auriculoventricular index.

The A-V ratio was first described in 1911 by Van Zwaluwenburg and Warren,<sup>2</sup> who drew, in addition to the long diameter of the cardiac silhouette (Fig. 1,  $DG'$ ), a line from the junction of the right auricle and the diaphragm to the junction of the pulmonary conus and the left ventricle ( $D'G'$ ). They admitted that this line did not represent exactly the auriculoventricular septum either in position or direction, but proceeded to assume that the two cardiac areas so produced roughly represented the auricular and ventricular areas. They then reasoned that if there were two similar segments, with a common base and the obliquity of the axis was equal, the areas would be in proportion to the fractional diameters  $DX$  and  $XG'$ , and that the ratio  $DX:XG'$  would roughly represent the surface relations of the auricles and ventricles.

Applying this new ratio to a small series of normal persons (number of cases not mentioned), they found that the normal values lay between 0.534 and 0.704. They then applied this ratio to a series of sixty abnormal hearts and found that all patients with mitral stenosis gave a value exceeding 0.880, even when complicated with mitral regurgitation. Patients with uncomplicated mitral regurgitation had values between 0.657 and 0.834. One patient with aortic insufficiency had a value of 0.378. The patients with arteriosclerosis had values between 0.282 and 0.393, due, the authors claimed, to the lengthening of the arch of the aorta, with a resulting low and transverse position of the heart. The value for one patient with arteriosclerosis was 0.492. This was considered to be a discrepancy and was explained on the basis of an irregular pulse.

From the Heart Station of the Rhode Island Hospital, Providence; Frank T. Fulton, M.D., Director.

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In 1920, Van Zwaluwenburg<sup>3</sup> again mentioned the A-V ratio, claiming the normal to be about 0.55. He stated that the largest ratio he had encountered was 1.42 (in a case of mitral stenosis) and that the smallest was 0.25 (in a well-compensated case of aortic regurgitation). At this time he presented an objection to the ratio, stating that the auriculo-diaphragmatic junction was not fixed and depended largely upon the height of the diaphragm.

In the same year Vaquez and Bordet<sup>4</sup> mentioned the work of Van Zwaluwenburg and Warren, but made no further observations or criticism of the A-V ratio.

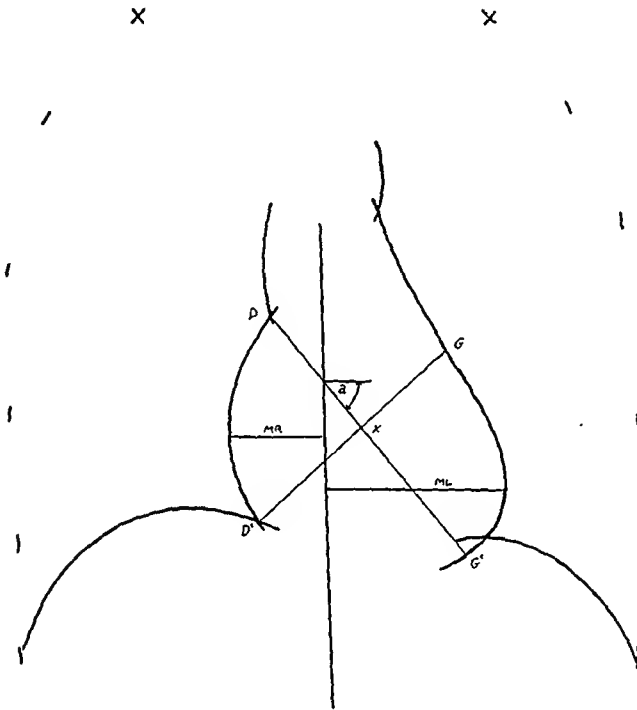


Figure 1.

The ratio was not mentioned again until 1932 when Levene and Reid<sup>5</sup> included it in an article concerning differential diagnosis of cardiac enlargement by use of the x-ray. They restated the normals attained by the previous writers, but arbitrarily chose values exceeding 0.800 as being indicative of auricular enlargement and values less than 0.500 as being caused by enlarged ventricles. An interesting table for differential diagnosis by means of roentgen ray measurement (modified from Vaquez<sup>6</sup>) was presented.

The same authors<sup>7</sup> in the same year stated that, contrary to popular belief, mitral stenosis occurs before mitral regurgitation in rheumatic heart disease affecting the mitral valve. They claimed that the old conception was due to the difficulty in recognizing early stenosis, and

they suggested as a means of diagnosis of early stenosis the use of the A-V ratio. They illustrated their theory with a series of patients supposed to have mitral stenosis, all having an increased A-V ratio. This material was entirely clinical, no pathologic evidence being presented.

With the material in these studies showing that conditions associated with left ventricular preponderance (arteriosclerotic heart disease, aortic insufficiency) had a low A-V index, and that mitral stenosis was associated with a high A-V index, it was only natural to wonder if there was any relationship between the A-V ratio and the electrical axis of the heart. This is a logical question because it had been shown that cases of the former type are associated with left axis deviation while those of the latter are associated with right axis deviation.

Weyler<sup>8</sup> studied a series of sixty-two cases with orthodiagrams and electrocardiograms made on the same day. The axis was determined by the method of Carter, Richter, and Greene.<sup>9</sup> He found, after statistical analysis of sixty-two cases, that there was a definite and direct correlation (by Pearson's coefficient of correlation;  $r = +0.75$ ) between these two values. He showed that left axis deviation was associated with a low A-V ratio while right axis deviation was associated with a high A-V ratio. He concluded that if the A-V ratio expressed the ratio between the auricles and ventricles, then right axis deviation must be due to enlargement of the auricles and left axis deviation to enlargement of the ventricles.

In considering the vast amount of material written about axis deviation and the x-ray study of the heart, one is impressed with the variety of opinion and realizes the necessity of separating facts from theories, work based on sound principles from that lacking such a fundamental groundwork.

Factual work concerning axis deviation has demonstrated a definite relationship between preponderance of one or the other ventricle, when the heart is markedly enlarged, and axis deviation.<sup>10-13</sup> Likewise, it has been shown that position of the heart in the chest exerts some influence on the electrical axis.<sup>11, 14-19</sup> It is probable that other factors also exist which exert a similar influence. It is certain that axis deviation is dependent upon more than one factor; that two of these factors are ventricular preponderance and position of the heart.

Other work,<sup>20</sup> logical, but not yet based upon sufficient evidence, proposes abnormalities of the conducting system to be a large factor in the determination of the electrical axis.

Factual work concerning roentgenology of the heart is scarce. Several studies are based upon autopsy findings,<sup>21, 22</sup> but, in general, this work is founded upon clinical impressions.

It is the general opinion that x-ray examination is not of sufficient accuracy in the determination of relative ventricular preponderance to

be of clinical use, but that it serves its most useful purpose in determining gross enlargement. For this latter purpose, estimation of the area of the cardiac silhouette and comparison with tables based upon prediction formulas are considered the best procedure.<sup>21, 22</sup> Comparison of the various diameters is not so good for this purpose, but is better for measuring deviations from normal in the shape of the heart.<sup>24</sup>

In general, the term "normal" should be discarded and replaced by "average." A value above average does not necessarily signify abnormality, but merely indicates that the individual patient has a greater chance of being abnormal than one found to be within the "average" group.

#### PROCEDURE

*General.*—This work is based upon a study of 300 cases, unselected except for technical reasons. Each patient was examined clinically and fluoroscopically. Orthodiascopy, immediately preceded or followed by an electrocardiogram, was performed. The A-V ratio of the cardiac silhouette was then calculated and compared with the electrical axis of the electrocardiogram. The cases were divided into groups of clinically normal and abnormal, and from this the average normal values of the electrical axis were determined. The cases were then divided into three additional groups—normal, right axis deviation, and left axis deviation—and the results concerning the relationship of the A-V ratio to axis deviation were subjected to mathematical analysis.

*Electrocardiographic Technique.*—Carter and Greene<sup>25</sup> claimed that the electrocardiogram was the only satisfactory clinical method of estimating the relative preponderance of the two ventricles, and added that it was useful when combined with teleroentgenography to determine gross hypertrophy. They claimed the potential of the excitatory process to be important in determining the electrical axis. This factor was considered when using Einthoven's triangle, but was ignored in using the various formulas. They further stated that, for the accurate determination of the angle of the axis, the records in the different leads should be synchronized to avoid phasic variations between the several derivations, and that the measurements should be taken at identical periods in the respiratory cycle. However, it was admitted that these refinements were usually neither possible nor desirable except in physiologic experimentation of the greatest exactitude. As a routine, they recommended taking an average of the measurements of several peaks, to obtain a mean value of the angle independent of respiratory variation. Usually these measurements obey the Einthoven law ( $E_1 + E_3 = E_2$ ), or else the error is so slight as to permit selection of a mean value of the angle. In a few cases where there was a marked discrepancy, the angle was determined from Leads I and III, Lead II being ignored. By this latter method the angle was accurate to within 5 degrees, and a greater degree of accuracy was thought to be unnecessary in ordinary clinical routine.

In the work of Weyler,<sup>8</sup> all cases were discarded in which the sum of Leads I and III did not equal Lead II. This is thought to be too exacting for work of this type.

In the majority of the cases in the present study, the findings were in accord with Einthoven's law. In a few, there was a discrepancy of several millivolts and, in view of the above findings, these cases were included in the study. It was felt that otherwise the limitations would exceed the physical equipment, because to do physiologic work of great exactitude, a three-string galvanometer,

capable of taking three simultaneous leads, is necessary.<sup>26</sup> This study, therefore, is primarily clinical.

The axis was determined by the method of Carter, Richter, and Greene.<sup>9</sup> In cases showing variation in the amplitude of the QRS complexes, apparently due to the respiratory cycle, several consecutive complexes were measured and a mean value was found, as recommended by White and Bock<sup>27</sup> and Carter and Greene.<sup>25</sup>

No children under 5 years of age were included, and no tracings were included in which the maximal deflection was less than 5 millivolts because of the unreliability of the electrical axis in these circumstances.<sup>28</sup> Cases of delayed interventricular conduction were discarded because the estimation of axis deviation is valueless in the presence of this abnormality.

Summary of the limitations shows: (1) no patients under 5 years of age; (2) no cases of delayed interventricular conduction; (3) no cases in which the maximal amplitude of the QRS deflection was less than 5 millivolts.

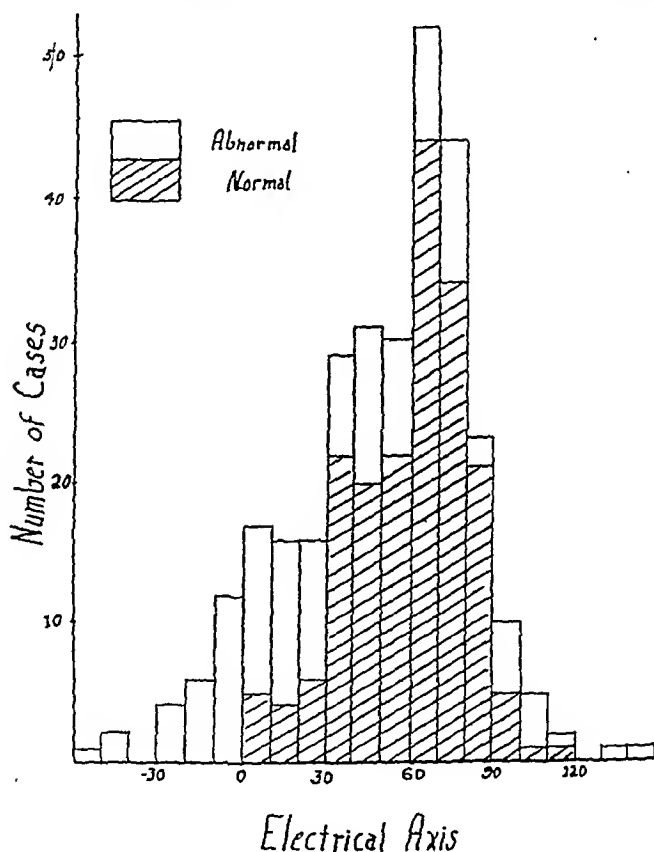


Fig. 2.

*Determination of Average Normal Limits.*—The 300 cases were divided into two groups, normal and abnormal, as determined by a thorough clinical examination (excluding the electrical axis). These were then charted (Fig. 2) according to the electrical axis. These values were analyzed,\* and it was found that if a normal

\*A Gram-Charlier frequency curve was fitted to the distribution of normal axis ( $y$ ). From this it was computed that, if normal axis was defined as " $y$ " from 20 to 90 degrees (less than 20, left axis deviation; more than 90, right axis deviation), more than 96 per cent of the clinically normal cases would fall in this range, subject to the condition, of course, that  $Fx$  represents the "true" distribution of " $y$ ."

Gram-Charlier frequency curve:

$$y = F(x') = \phi(x') + 0.0668 \phi^3(x') - 0.0990 \phi^4(x').$$

$\phi(x)$  represents the normal curve;  $\phi^2(x)$  its first derivative; and so forth.

$$x' = \frac{x - \bar{x}}{\sigma x}$$

axis was considered to be from 20 to 90 degrees (as determined by Einthoven's triangle), 96 per cent of the normal patients would fall in this range.

In this work, for the purpose of mathematical analysis, the normal axis was considered to be from 20 to 90 degrees, values below 20 degrees indicating left axis deviation and values above 90 degrees indicating right axis deviation.

*Roentgenologic Technique.*—Fluoroscopy of the chest and heart was performed after the examiner's eyes were accommodated. All of the orthodiagrams were made by one operator, which eliminated the error due to the variation between the work of several different individuals. The orthodiagram was made with the patient standing and facing the operator, with the screen held fixed against the patient's chest. The tube was then moved around the cardiac and thoracic silhouettes and the tracing was made upon a glass plate held firmly in contact with the fluoroscopic screen by clamps. The tracing was later transferred to a piece of semitransparent paper from which the measurements were taken.

As recommended by Roesler,<sup>20</sup> the tracing was made during quiet respiration when the diaphragm was in its most cephalad position. Bardeen<sup>21</sup> recommended having the patient drink several glasses of water prior to the examination, swallowing all the air possible in order to form an air bubble in the stomach and facilitate visualization of the apex. This might be satisfactory in routine work, but could not be used here as it produced an elevation of the left dome of the diaphragm, causing a shift of the anatomic axis which, as will be shown later, would have affected all of the measurements under consideration in this study. The cardiac silhouette was traced during diastole, and the area of the great vessels during systolic contraction of the ventricles, thus obtaining the largest possible silhouette.

All cases in which pulmonary disease or other conditions precluded accurate determination of the cardiac silhouette were discarded.

The orthodiagram was measured in the usual manner (Fig. 1). The transverse diameter was taken to be the sum of *MR* (perpendicular from the midline to the most distant point on the right auricle) and *ML* (perpendicular from the midline to the most distant point on the left ventricle). The long diameter (*DG'*) was drawn from the auriculo-great-vessel junction on the right to the apex. Roesler<sup>20</sup> and others<sup>2, 21, 30-33</sup> considered the apex to be the furthestmost point at the left lower pole. In the work of Levene and Reid,<sup>5</sup> the long diameter was drawn to the junction of the left ventricle and the diaphragm, which, plus the fact that their work was done with teleroentgenograms, explains to some extent the discrepancies between their results and the results of the present study.

A line (*D'G*) was drawn from the junction of the right auricle and the right dome of the diaphragm to the auriculoventricular junction on the left cardiac border. This line, according to some observers,<sup>1, 2, 4, 5, 8</sup> corresponds roughly to the position of the auriculoventricular septum. The A-V ratio was obtained by dividing the length of the long axis (*DG'*) above the point of bisection (*DX*) by the portion below this point (*XG'*).

The angle of inclination, or the anatomic axis, was taken to be the angle between the long axis and the horizontal, the measurement beginning at the left.

#### COMPARISON OF ORTHODIAGRAMS WITH TELEROENTGENOGRAMS

The purpose of this study is obvious. The work of Van Zwaluwenburg and Warren<sup>2</sup> was done by orthodiascopy, the apex being used as the lower pole of the longitudinal axis. The work of Levene and Reid<sup>5</sup> was based upon 7-foot plates and the lower pole of the long axis was taken to be the junction of the left ventricular shadow and the left dome of the diaphragm. The work of Weyler<sup>8</sup> was based upon orthodiagrams.





Several workers<sup>23, 34</sup> have reported the average magnification of the cardiac shadow on a 7-foot plate. Their results were variable. It was desired to determine: (1) the amount of magnification obtained in our clinic; (2) the effect of the respiratory phase in a series of cases; and (3) the effect, if any, of these factors on the A-V index.

The work of Hodges<sup>34</sup> was done with the patient seated in front of a piece of apparatus which permitted centering of the patient under fluoroscopic visualization, followed by a 7-foot plate and orthodiascopy without any change in position on the part of the patient. These conditions were as nearly ideal as could be hoped for in a problem of this type, and the results, expressed in percentage relations between cardiac silhouette areas, are definite and authoritative.

The present series of fifteen normal persons were subjected to electrocardiography, orthodiascopy, and teleroentgenography, the examinations taking place in succession and as rapidly as routine work permitted. There were two 7-foot plates taken of the chest; one taken with the usual chest technique, i.e., with the patient holding the breath in deep inspiration, and the other taken during quiet respiration in an attempt to simulate the conditions obtained during orthodiagraphy.

TABLE II

DIFFERENCE BETWEEN	MINIMAL	MAXIMAL	AVERAGE
Transverse diameter:			
O and N	0.5 cm. 5%	1.8 cm. 16%	1.1 (1.09) cm. 10 (10.1) %
N and I	0 0	1.3 cm. 9%	0.5 (0.51) cm. 4 (4.06) %
O and I	0.2 cm. 2% -0.2 cm. -1%	1.2 cm. 12% -0.3 cm. -3%	0.7 (0.707) cm. 6 (6.3) % -0.25 cm. -2%
Angle of inclination:			
O and N	3°	21°	10 (9.53)°
N and I	2°	14°	6 (6.06)°
A-V index:			
O and N	.018	.344	.112
N and I	.004	.237	.103
O and I	.001	.334	.090

Again, with consideration of the technical flaws in this procedure, it was nevertheless believed to give pertinent and presentable data because (1) the technique was the same as in the usual routine examination and (2) the results were consistent regarding changes in the transverse diameter of the heart, the transverse diameter of the thorax, the cardiothoracic ratio, and the angle of inclination (anatomic) of the heart with the horizontal.

The results of the examinations in these fifteen cases are seen in Table I. The study of the transverse diameter of the heart, with a comparison of the values obtained by the different methods, is of primary importance.

In comparing the values, it was found that, without exception, those obtained by the 7-foot plate during quiet respiration exceeded those obtained by orthodiascopy. As shown in Table II, the maximal difference was 1.8 cm. (16 per cent), and the minimal 0.5 cm. (5 per cent), with an average of 1.1 cm. (10 per cent). These figures are valuable in that they demonstrate the results obtained in this clinic to be (1) consistent and (2) comparable with findings obtained elsewhere.

In comparing the values of the transverse diameter of the heart as obtained by the 7-foot plates, the variable being the respiratory phase, it was found that the values obtained during quiet respiration exceeded those obtained during forced inspiration with but one exception.\* The minimal decrease was zero; the maximal 1.3 cm. (9 per cent). The average decrease was 0.5 cm. (4 per cent). It may be positively stated that no value obtained during quiet respiration was less than any value obtained at the end of inspiration. This was easily explained by the fact that a high diaphragm (present during quiet respiration) tends to produce a transverse position of the heart, while a low diaphragm (present with deep inspiration) tends to make the heart assume a vertical position.

The difference in the values of the transverse diameter obtained by orthodiagraphy and teleroentgenography (plate taken during inspiration) are valuable from a practical standpoint; i.e., the latter method is the routine technique for taking chest plates in most laboratories and much work in regard to cardiac mensuration is based upon such plates. The values obtained by the use of the 7-foot films were greater than those of the orthodiagrams, with but two exceptions. These exceptions may be explained when the great number of variable factors involved are considered, the two foremost factors being the magnification of the plate over the orthodiagram and the decrease in the transverse diameter with inspiration. Other factors to be considered are depth of respiration, etc. The maximal difference was 1.2 cm. (12 per cent); the minimal, 0.2 cm. (2 per cent); the average, 0.7 cm. (6 per cent).†

The angle of inclination made by the long axis of the heart with the horizontal was, in all cases, smaller in the teleroentgenogram (normal respiration) than in the orthodiagram. The maximal difference was  $21^{\circ}$ ; the minimal,  $3^{\circ}$ ; the average,  $10^{\circ}$ . The value of the angle between quiet respiration and deep inspiration likewise showed consistent results, all of the latter being greater than the former. The maximal difference was  $14^{\circ}$ ; the minimal,  $2^{\circ}$ ; the average,  $6^{\circ}$ .

The former comparison (between the angle on the orthodiagram and 7-foot plate) is not valid because, in the former, the apex is used as the

\*This was a case in which the changes were minimal in all of the observations. It is assumed that the patient did not use the diaphragm to full advantage in the act of respiration.

†These values were calculated by considering only the thirteen positive values. The two negative values of 0.2 and 0.3 cm. averaged 0.25 cm.

lower pole of the axis, while in the latter, the junction of the left ventricle with the diaphragm is utilized for this purpose. The comparison is included only for its practical interest. On the other hand, the comparison of the two films is between two values which differ only in the phase of respiration. These figures are of definite value.

The long axis will be mentioned here merely as a preliminary to a study of the A-V index. This value (L) is subject to the same criticism as is presented in the preceding paragraph. It will be noted that, as this subject is being developed from the simple to the complex (i.e., from an initial study of transverse diameter to a final consideration of the A-V index), the number of conditioning factors becomes multiplied with each step. The long axis, with five exceptions, is greater in the normal teleroentgenogram than in the orthodiagram, and still greater in the teleroentgenogram taken during forced inspiration. These five exceptions are minor and are not consistent in regard to the type of case affected (i.e., transverse or vertical heart, high diaphragm, etc.) and serve to bring out the multitude of further conditioning factors involved. Some of the factors are the magnification due to the 7-foot plate, change in the anatomic angle with respiration, and, of maximum importance, difference in the selection of the lower pole of the cardiac long axis.

The A-V index as computed from the film taken during quiet respiration was smaller than the value computed from the orthodiagram, with five exceptions. The minimal variation was 0.018; the maximal, 0.344; and the average, 0.112.

The effect of respiration upon the A-V index was somewhat less. A comparison of the values as computed during quiet respiration and at the end of forced inspiration (both films) showed that the values of the latter were greater than those of the former, with four exceptions. The minimal variation was 0.004; the maximal was 0.237; and the average, 0.103.

A comparison of the values of the A-V index as computed from the orthodiagram and the film taken during forced inspiration shows that the values of the former are less than those of the latter, with four exceptions. The minimal variation was 0.001; the maximal was 0.334; and the average, 0.090.

The exceptions in the three preceding paragraphs did not all occur in the same four or five cases, but were distributed through nine cases, giving a disagreement in nine of fifteen cases. Furthermore, it should be noted that Cases 117 and 100 show differences of 0.344 and 0.327, respectively, between the A-V ratios as determined by the orthodiagram and the film during quiet respiration. Case 117 shows a difference of 0.334 between the value obtained by the orthodiagram and that obtained by the film during inspiration. These three values are in excess of the range of normality (0.300) as expressed by Levene and Reid,<sup>5</sup> who accepted 0.500 to 0.800 as the limits of normal.

It was considered unnecessary to submit these results to statistical analysis because, as shown above, it was evident that the changes were consistent in the case of all the values except the A-V index.

The results of this study suggest that: (1) with the exception of the A-V index, most of the usual cardiac measurements show differences due to technique which can be predicted and are, more or less, constant; (2) results obtained by one technique are comparable only with other results obtained by the use of the same technique; (3) the A-V index is unreliable as a cardiac measurement.

### RESULTS

The 300 cases were divided into two groups, normal and abnormal, according to clinical findings. The electrical axis and the A-V index for each case were recorded in Table III. A scatter diagram (Fig. 3) based upon these results is presented. A high degree of correlation, if present, would tend to cause the dots to approach a straight line. Such is not the case in this instance, as the dots are widely scattered.

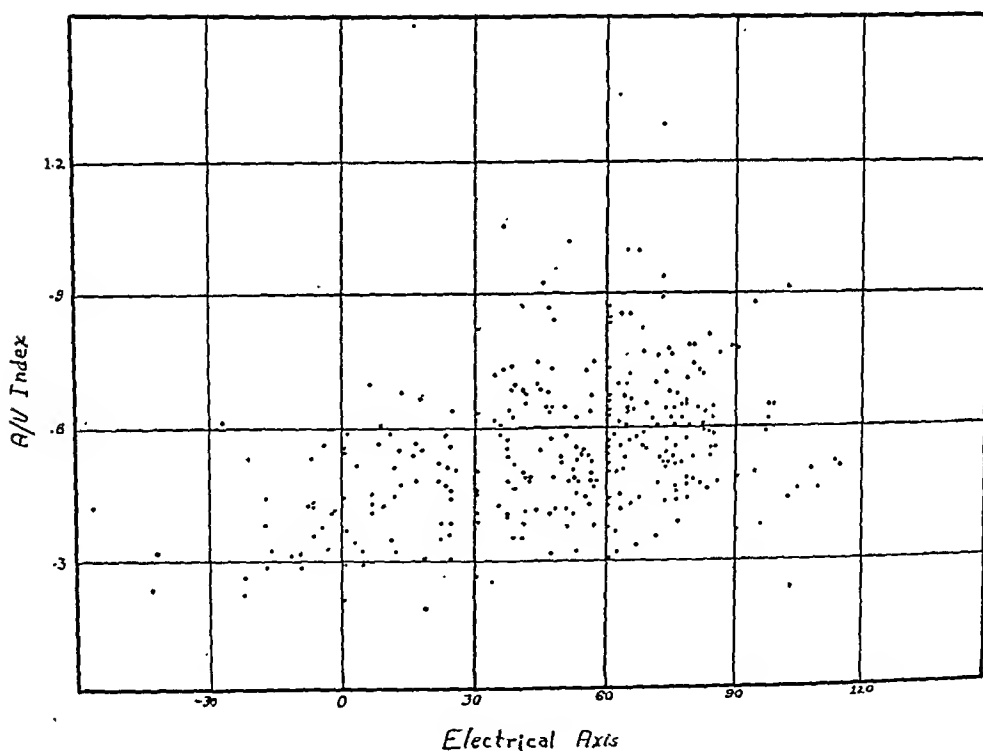


Fig. 3.

The results were subjected to statistical analysis. The cases were divided into the following groups, and the correlation between the axis and the A-V index was determined for each group:

1. Normal clinically; no significant correlation.
2. Abnormal clinically;  $r = 0.400$ .
3. Left axis deviation; no significant correlation.
4. Right axis deviation; no significant correlation.
5. Normal axis;  $r = 0.303$ .

TABLE III

NO.	AXIS	A-V	NO.	AXIS	A-V
<i>Clinically Normal Cases</i>					
1	75	0.688	59	72	0.541
2	23	0.472	60	37	0.531
3	76	0.600	61	77	0.397
4	79	0.792	62	62	0.500
5	73	0.522	63	97	0.652
6	65	0.601	64	39	0.734
7	73	0.535	65	66	0.326
8	49	0.531	66	7	0.458
9	47	0.481	67	56	0.552
10	60	0.303	68	79	0.577
11	73	0.641	69	16	0.569
12	25	0.516	70	38	0.731
13	63	0.867	71	85	0.542
14	47	0.667	72	49	0.732
15	50	0.581	73	65	0.802
16	44	0.697	74	60	0.739
17	73	0.896	75	83	0.605
18	75	0.613	76	56	0.444
19	84	0.461	77	57	0.487
20	42	0.493	78	30	0.505
21	57	0.737	79	75	0.523
22	30	0.462	80	85	0.624
23	47	0.631	81	35	0.612
24	57	0.543	82	40	0.693
25	17	0.541	83	36	0.423
26	65	0.702	84	97	0.614
27	87	0.772	85	69	0.593
28	65	0.641	86	65	0.634
29	66	0.638	87	52	0.408
30	39	0.615	88	58	0.530
31	113	0.529	89	64	0.661
32	80	0.482	90	65	0.728
33	65	1.000	91	25	0.439
34	75	0.769	92	102	0.912
35	79	0.600	93	82	0.477
36	60	0.836	94	56	0.486
37	79	0.711	95	49	0.549
38	36	0.601	96	60	0.652
39	78	0.662	97	85	0.589
40	60	0.549	98	76	0.569
41	85	0.564	99	50	0.378
42	68	0.771	100	63	0.705
43	63	0.865	101	75	0.544
44	57	0.475	102	30	0.398
45	60	0.500	103	57	0.628
46	45	0.927	104	52	0.511
47	69	0.645	105	80	0.746
48	84	0.630	106	78	0.561
49	54	0.545	107	80	0.540
50	77	0.528	108	78	0.654
51	53	0.538	109	37	0.482
52	73	0.526	110	60	0.455
53	60	0.671	111	65	0.574
54	39	0.701	112	74	0.434
55	7	0.704	113	79	0.455
56	45	0.555	114	81	0.648
57	44	0.416	115	80	0.786
58	84	0.591	116	38	0.355

TABLE III—CONT'D

NO.	AXIS	A-V	NO.	AXIS	A-V
117	60	0.541	152	87	0.477
118	63	0.605	153	37	0.573
119	68	1.000	154	62	0.871
120	70	0.621	155	7	0.434
121	53	0.324	156	37	0.400
122	63	0.563	157	63	0.421
123	90	0.771	158	71	0.352
124	72	0.488	159	60	0.434
125	36	0.588	160	63	0.466
126	65	0.426	161	90	0.493
127	69	0.565	162	54	0.563
128	57	0.500	163	55	0.456
129	47	0.884	164	30	0.632
130	25	0.640	165	41	0.417
131	60	0.636	166	24	0.591
132	60	0.662	167	52	0.493
133	36	1.059	168	74	0.725
134	57	0.674	169	71	0.702
135	60	0.573	170	49	0.494
136	90	0.772	171	13	0.563
137	72	0.761	172	30	0.272
138	60	0.887	173	40	0.352
139	83	0.597	174	25	0.456
140	85	0.646	175	67	0.588
141	43	0.700	176	42	0.493
142	4	0.529	177	76	0.453
143	41	0.659	178	87	0.402
144	69	0.563	179	39	0.464
145	83	0.716	180	38	0.638
146	62	0.586	181	67	0.448
147	71	0.600	288	19	0.186
148	75	0.641	289	79	0.495
149	40	0.696	290	84	0.808
150	54	0.621	299	38	0.512
151	1	0.588			

<i>Clinically Abnormal Cases</i>					
182	48	0.421	205	77	0.684
183	21	0.489	206	74	1.272
184	50	0.420	207	98	0.651
185	25	0.353	208	23	0.343
186	56	0.726	209	12	0.452
187	102	0.448	210	47	0.411
188	-8	0.434	211	62	0.806
189	114	0.519	212	7	0.414
190	0	0.567	213	-12	0.306
191	-17	0.389	214	9	0.431
192	-10	0.312	215	9	0.600
193	19	0.665	216	-6	0.540
194	53	0.463	217	74	0.591
195	35	0.265	218	42	0.494
196	57	0.382	219	25	0.561
197	-22	0.231	220	5	0.296
198	30	0.458	221	58	0.488
199	65	0.532	222	48	0.851
200	-1	0.426	223	5	0.327
201	30	0.824	224	8	0.562
202	0	0.291	225	48	0.290
203	40	0.500	226	20	0.270
204	-16	0.287	227	-3	0.333

TABLE III—CONT'D

NO.	AXIS	A-V	NO.	AXIS	A-V
					0.323
228	13	0.475	263	47	0.450
229	-26	0.611	264	-17	0.423
230	50	0.649	265	-7	0.558
231	13	0.684	266	38	0.659
232	46	0.688	267	46	0.594
233	-19	0.300	268	145	0.524
234	62	0.319	269	21	0.541
235	2	0.369	270	-21	0.433
236	-41	0.321	271	-56	0.481
237	-5	0.391	272	79	0.615
238	51	1.023	273	78	0.209
239	10	0.590	274	0	0.437
240	11	0.353	275	-7	0.562
241	36	0.724	276	0	0.883
242	108	0.504	277	94	0.667
243	63	0.612	278	63	0.622
244	60	0.518	279	60	0.510
245	-43	0.236	280	27	0.380
246	109	0.462	281	96	0.370
247	77	0.650	282	90	0.516
248	0	0.446	283	11	0.379
249	73	0.932	284	60	0.555
250	74	0.773	285	18	0.753
251	23	0.387	286	44	0.414
252	51	0.488	287	30	0.463
253	41	0.386	291	104	0.568
254	-22	0.267	292	86	0.581
255	-10	0.298	293	-3	0.698
256	-1	0.426	294	38	0.722
257	25	0.389	295	130	0.591
258	12	0.322	296	96	0.739
259	-16	0.318	297	81	0.469
260	25	0.304	298	76	0.489
261	73	0.466	300	17	
262	-6	0.363			

6. Normal axis and normal clinically; no significant correlation.

7. Normal axis and abnormal clinically;  $r = 0.630$ .

Groups 2, 5, and 7, taken together, show that there is a true correlation of fairly high magnitude between the electrical axis and the A-V index in the group of abnormal cases with a normal electrical axis. The correlations shown in Groups 2 and 5 are results of the fairly high correlation found in Group 7 where the variables are classified in the above manner. Group 5 is only a real correlation inasmuch as it reflects Group 7, since clinically normal and abnormal cases are not statistically homogeneous\* and there is no legitimate reason for combining them.

\*The clinically normal cases showed a mean A-V index of 0.589 and a mean axis of 53.903. The clinically abnormal cases showed a mean A-V index of 0.504 and a mean axis of 53.770. The means were found to be significantly different:

A-V index	$D = 0.085$	$\sigma D = 0.02041$
Axis	$D = 25.133$	$\sigma D = 4.0395$

( $D$  = difference between the respective means;  $\sigma D$  is a measure which shows the range of probability of getting the measure  $D$  as a result of pure chance. When any measure is greater than 3.5 or 4.0 times its own standard deviation ( $\sigma$ ), it is said to be significant; i.e., the probability that this measure will occur as a result of pure chance in picking the sample is very small.)

This shows the clinically normal cases to be different with respect to the two measures (axis and A-V index) under consideration than the clinically abnormal cases.



*Conclusion (Statistical).*—There exists a fairly high, valid correlation between the electrical axis and the A-V index in the group of cases that are clinically abnormal with normal electrical axes ( $r = 0.630$ ). There is no significant correlation between the electrical axis and the A-V index in any of the other classes.

#### DISCUSSION

The largest A-V ratio encountered by Van Zwaluwenburg<sup>3</sup> was 1.42 (in a case of mitral stenosis); the smallest, 0.25 (in a case of aortic regurgitation). In the present study, none were encountered as great as 1.42, but there were four ratios less than 0.25.\* Case 288 was a young woman, perfectly normal except for obesity. The chest was of the short, thick type, and the diaphragm was high, which caused the heart to lie in an extreme transverse position. The electrical axis was  $19^\circ$ . The blood pressure was within normal limits, as were the findings in the remainder of the physical examination. Case 197 was a 65-year-old man with hypertensive and arteriosclerotic heart disease. Case 245 was a 35-year-old man with clinical and electro cardiographic evidence of a recent anterior coronary occlusion, whose orthodiagram was that of a normal transverse heart. Case 274 was a 57-year-old man with evidence of an old coronary occlusion and enlargement of the left ventricle on the basis of arteriosclerosis and hypertension. The above cases do not constitute sufficient evidence upon which to base any conclusions; they are presented only for completeness.

It is noteworthy that the cases presented by Van Zwaluwenburg gave, in general, higher values for the A-V index than the cases studied in this present work. Van Zwaluwenburg stated the normal *limits* of the A-V index to be 0.534 and 0.704. In the present work, the *mean* value of the normal cases was 0.589, which is very close to Van Zwaluwenburg's lower limit of normal. This fact is difficult to explain because both studies were based upon the orthodiagram, and, in both instances, the long axis was drawn to the apex. Van Zwaluwenburg did not mention the number of cases in his series. If this was small, it would limit the value of the study and explain, at least partially, the difference between his results and the results of this study.

Van Zwaluwenburg and Warren<sup>2</sup> claimed that every case of mitral stenosis gave a value for the A-V index above 0.880, even when the stenosis was complicated by regurgitation. In the present study, there were sixteen cases of definite mitral stenosis.† Of these, ten were complicated by mitral regurgitation; two by aortic regurgitation; and two by aortic stenosis. Only two of the sixteen cases gave an A-V index of more than 0.880, and both of these were complicated by mitral regurgitation. The two lowest values were 0.382 and 0.389, found in cases

\*Case 288 = 0.186; Case 197 = 0.231; Case 245 = 0.236; Case 274 = 0.209.

†Cases 186, 187, 191, 196, 207, 211, 221, 222, 232, 238, 242, 261, 273, 277, 279, and 294.

complicated by aortic stenosis and regurgitation, respectively. The average value of the A-V index for the sixteen cases of mitral stenosis was 0.646.

On the other hand, there were eleven definitely normal cases<sup>6</sup> with A-V indices above 0.800, eight of them being above 0.880. All of these were normal hearts of the vertical type, i.e., in a person with a long, narrow chest. This should make one extremely cautious in using the A-V index as a method for the diagnosis of early mitral stenosis, as recommended by Reid and Levene.<sup>7</sup>

The work of Weyler<sup>8</sup> was based upon orthodiagrams made by several different operators. This introduced the factor of personal technique, which, however, should produce but slight differences in the various measurements. However, his work is open to criticism concerning the total number of cases. A series of sixty-two cases is too small a number from which to expect valid conclusions from statistical analysis.

#### SUMMARY AND CONCLUSIONS

A study was made of the A-V index of the cardiac silhouette as to its nature, its general usefulness, and, specifically, its relationship to the axis of the electrocardiogram.

The data concerning the A-V index and the electrical axis in 300 unselected cases were subjected to mathematical analysis. The cases were separated into two clinical groups, normal and abnormal, and the average limits of the normal electrical axis determined. Fifteen normal subjects were studied, in addition to the above procedures, by the means of two teleroentgenograms, one taken during quiet respiration and the other after deep inspiration. The values so obtained were studied to determine the relationship of the various cardiac measurements as obtained by the different techniques.

The following conclusions were reached:

1. In general, there is no valid correlation between the A-V index and the electrical axis of the heart. The A-V index is of no clinical importance and bears no definite relationship to mitral stenosis, and is neither reliable nor consistent as a cardiac measurement.

2. The limits of normal in regard to the electrical axis of the heart should not be used dogmatically. An abnormal value does not always mean an abnormal heart, but merely indicates that the possibility of the heart's being abnormal is greater than in a case with a normal value for the axis.

3. As determined by statistical methods, 20 to 90° (Einthoven's triangle) is the most satisfactory average normal range for the electrical axis.

<sup>6</sup>Cases 13, 17, 33, 43, 46, 73, 92, 119, 129, 133, and 154.

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## LIVEDO RETICULARIS: A PERIPHERAL ARTERIOLAR DISEASE

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**L**IVEDO reticularis is a term which has been used to describe a local circulatory disorder characterized by a mottled, blotchy or reticular, bluish discoloration of the skin. There is usually subjective and objective coldness of the skin, and the color of the blotches may vary from rather deep blue when the patient is in a cold environment, to red or reddish purple when he is in a warm environment. The condition has also been described under the terms "livedo racemosa," "livedo annularis," and "asphyxia reticularis." The literature on the subject is somewhat confusing, but good descriptions and discussions have been given by Adamson,<sup>1</sup> Williams and Goodman,<sup>2</sup> Becker,<sup>3</sup> and Ebert.<sup>4</sup> The term "livedo reticularis" seems to have superseded the other terms in recent years.

Williams and Goodman have divided cases of livedo reticularis into three groups, namely, (1) *cutis marmorata*, a rather commonly observed mottling of the skin on exposure to cold which disappears when the patient is brought into a warm environment, and seems to be unassociated with any other disease; (2) *livedo reticularis idiopathica*, in which the bluish mottling is more intense and persists in spite of changes of temperature, although there may be variations in the mottling; in this group there is no evidence of any associated disease; in most of the cases which Williams and Goodman<sup>2</sup> place in this category the patients were children, and many had congenital defects elsewhere in the body; and (3) *livedo reticularis symptomatica*, in which the mottling is also persistent; in this group there is evidence of some other disease which affects the cutaneous and subcutaneous vascular system. In this category have been placed livedo reticularis associated with the erythema induratum type of tuberculids of the lower extremities, which was described by Adamson,<sup>1</sup> and those cases in which it was associated with syphilis, as described by Ehreman.<sup>5</sup> In these two groups definite inflammatory changes have been demonstrated in the arterioles of the subcutaneous tissue. Recently, Ketron and Bernstein<sup>6</sup> described a case, with necropsy studies, in which extensive livedo reticularis was associated with periarteritis nodosa.

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In 1922, Stokes<sup>7</sup> described a case of typical livedo racemosa (livedo reticularis) which had first appeared when the patient was 27 years old. There was no evidence of tuberculosis or syphilis, but biopsy revealed obliteration of some of the larger arterioles. A similar case was described by Becker,<sup>8</sup> who found perivascular lymphatic infiltration and adventitial fibrosis, in addition to the intimal proliferation. In another case described by Becker, biopsy of the skin showed very few changes



Fig. 1.—Case 11. Uncomplicated livedo reticularis, showing typical mottling and the usual involvement of feet and legs to knees.

other than a slight lymphocytic periarteriolar infiltration. This patient had hypertension and hyperthyroidism with an adenomatous goiter. The influence of these conditions as an etiological factor is doubtful. Ebert<sup>4</sup> reported a case of extensive livedo reticularis, associated with

recurrent ulcerating nodules of the legs. Biopsy revealed marked inflammatory changes in the arterioles and small arteries, with perivascular lymphocytic infiltration, intimal proliferation, and thrombosis of some of the small veins. Ebert considered his case as one of permanent livedo reticularis, probably associated with tuberculids. However, he was not able to find other evidence of tuberculosis; the histologic changes were not entirely typical of tuberculid; and the tuberculin reaction of the skin was negative. Ebert himself questioned whether true tuberculosis was the etiologic factor.



Fig. 2.—Case 4. Livedo reticularis with necrotic ulcers of right leg.

It is probable that livedo reticularis should not be considered as a disease entity, but rather as a circulatory phenomenon. It is also probable that the physiologic disturbance which manifests itself as livedo reticularis may be produced by different diseases, some known and some unknown, just as Raynaud's phenomenon may occur as the result of

cervical rib, thromboangiitis obliterans, or scleroderma, or may occur in the absence of any of these diseases and be called simply Raynaud's disease.



Fig. 3.—Case 2. Livedo reticularis with gangrene of distal half of right second toe and healed gangrene of skin of left third toe.

We wish to report a series of thirteen cases of livedo reticularis. All of these patients had a persistent bluish to bluish-red mottling of the skin of both legs and feet (Fig. 1). In some instances this mottling extended also to the thighs; it involved the hands and arms to a less degree, and even the lower part of the trunk. The livedo was more noticeable when the patients were exposed to cold, and there was a persistently lowered temperature of the skin. The age at onset varied from 21 to 47 years. There was no evidence of syphilis, tuberculosis, or tuberculids in any of the cases. Also, there was no evidence of occlusive



TABLE I  
DATA ON CASES OF LIVEDO RETICULARIS

CASE NO.	AGE (YR.)	SEX	EXTENT OF LIVEDO RETICULARIS	DURATION OF LIVEDO RETICULARIS (YR.)	GANGRENE, ULCERATION, OR ARTERIAL OCCLUSIONS	SUBJECTIVE SYMPTOMS	BLOOD PRESSURE ON ADMISSION (MM. OF MERCURY)	ASSOCIATED CONDITIONS
1†	34	M	Progressively, legs, feet, thighs, arms, and lower part of trunk	8	Recurrent painful ulcers of legs, intractable to treatment; a c u t e arterial occlusions of both first toes, without gangrene	Coldness, numbness, paresthesias; severe pains in ulcers and in first toes at time of arterial occlusion	115/64	Questionable lead poisoning at onset, not confirmed later; peripheral neuritis, nervous instability, anxiety neurosis, and narcotic addiction
2†	34	M	Legs and lower part of thighs	1	Two attacks of superficial gangrene, distal half of right, second toe	Cold feet; severe pain in gangrenous toe	135/85	Frost bite five years before onset; severe sore throat at onset of livedo
3	31	M	Progressively, feet, legs, hands, and left arm	3	Five attacks of superficial gangrene of toes, R2 (twice), R4, L3, L4	Coldness; severe pain in gangrenous toes for two to three months	125/85	Gangrene usually preceded by mild trauma
4	25	M	Both feet and legs below knees	4	Recurrent ulcers of lower legs, usually after injury	Coldness; mild to moderate pain in ulcers	114/76	Lead found in urine

\*This case has been reported previously in detail.<sup>8</sup>

†Sympathetic ganglionectomy was performed in these cases.

5+	39	M	Both feet and legs below knees	2	Gangrene and amputation R2 toe, gangrenous ulcer R1 toe, lateral aspect right foot	Marked coldness of feet and legs, with aching, in cold weather; severe pain in gangrenous toes and ulcer	200/130	Labile blood pressure; minimal retinal arteriosclerosis; pains in ankles and wrists, with some swelling
6	37	F	Both feet and legs to knees, few areas on arms	14	One small ulcer lower leg	Coldness, aching, swelling in hot weather	124/78	Obesity
7	46	F	Both legs to mid-thighs, both arms above elbows	Uncertain	0	Slight swelling of ankles	116/78	Hypertension twice during toxemias of pregnancy; two cerebral vascular accidents
8	35	M	Both feet and legs to knees	4	0	0	156/104	Cerebral vascular accident, with hemiplegia
9	47	M	Both feet and legs to knees	1	0	Coldness, aching, burning, numbness	160/102	Arsenic found in urine; peripheral neuritis, nervous instability, anxiety neurosis
10	50	F	Progressively, both feet, legs, thighs, lower part of abdomen, left arm	6	0	Coldness, aching especially when dependent; relief with heat and elevation	150/90	Positive tourniquet test, no abnormalities of the blood
11	37	F	Both feet and legs to knees	Uncertain	0	Coldness, aching, numbness	126/75	Menopause, nervous instability
12	56	F	Both feet and legs to knees	30?	0	Slight aching	170/114	Brain tumor (meningioma)
13	40	F	Both feet and legs to knees	4	0	Coldness	158/110	Carcinoma of breast, nervous instability

disease of the larger arteries such as the dorsalis pedis, posterior tibial, and popliteal arteries, and there were no varicose veins or clinical features of ordinary venous insufficiency. The essential data in these cases are given in Table I.

In addition to the livedo, recurring ulceration of the skin of the legs, which, the patients felt, began as an intensification of an area of bluish discoloration, had developed in three cases (Fig. 2). In two of the three cases the ulcers were very resistant to treatment, and in all three they were very painful. In the case in which there was the most extensive ulceration, occlusion of the arteries of each great toe also developed on separate occasions. This was characterized by sudden pain, pallor, and marked decrease in skin temperature which persisted for several weeks. In three other cases there was a peculiar type of gangrene of the skin of the toes, characterized by a fairly sudden onset of purplish-black discoloration and moderately severe pain which persisted for several weeks or months and involved the distal half to the entire toe (Fig. 3). In each instance the skin ultimately became black and hard and finally sloughed, with healing except in one case in which it was necessary to amputate the toe because of nonhealing and severe pain.

#### COMMENT

*Etiology.*—We were unable to demonstrate a common etiological factor in our group of cases. Of the thirteen patients, six were women and seven were men. It is interesting, however, that, of the six cases of ulceration and gangrene, five occurred in men, and the one that occurred in the woman was a comparatively small, benign ulcer. All but one of the men were mild to moderate smokers. All but one of the women were nonsmokers. All but one (a man, Case 3) who had ulceration or gangrene were smokers. In four of the thirteen cases there was moderate hypertension, and, in one other case, there was a history that hypertension had occurred twice in association with toxemias of pregnancy. In this case and in one other in which there was hypertension, cerebral vascular accidents had occurred at relatively early ages (35 and 38 years). In a few other cases in the literature, livedo reticularis has been observed in association with hypertension, arteriosclerosis, and heart disease. However, it is probable that these vascular disorders are coincidental, rather than etiological factors. They may indicate a tendency toward vulnerability of the vascular system as a whole.

In one of our cases there was a history of exposure to arsenic, and arsenic was found in the urine. One patient had an indefinite history of lead poisoning at the onset of the livedo, but no lead was found in the urine at the time of our examination. Another patient had no history of lead poisoning, but lead was found in the urine at the time of our examination. In three other cases the urine was examined for lead, but the results of examination were negative. One patient had a his-



livedo. In two of our cases a rather marked change was observed after the subcutaneous injection of 10 mg. of meeholyl (acetyl-beta-methylcholine chloride). The usual weakness, tremor, and salivation developed, and, within five minutes, the skin of the lower extremities became definitely pink; this began in the thighs, and progressed slowly to the tarsal regions. As this pink wave spread over the skin the livid areas were completely obliterated, and the patients stated that this was the first time that this had been noted since the onset of the disorder. The effect was not apparent in the distal portions of the feet. Following the pink wave the skin became pale, but the areas of livedo did not reappear for from one to three hours. Typhoid vaccine was administered to four of our patients, and this caused an elevation of systemic temperature and a rise of skin temperature in the toes and legs to 32° C. or more, indicating fairly complete vasodilatation. During these periods the livedo was somewhat less noticeable, but it did not completely disappear.



Fig. 4.—Case 6. Biopsy specimen of skin and subcutaneous tissue, showing arterioles with thickened walls and many perivascular lymphocytes (photomicrograph  $\times 175$ ).

Lumbar sympathetic ganglionectomy was followed by a change of the color of the livid areas to pink, except on exposure to extreme cold in one of our cases (Case 1), and by almost complete disappearance of the livedo in the sympathectomized parts in two other cases (Cases 2 and 5). The available evidence would indicate that there is spasm of the arterioles of the skin in the areas where the livedo exists, but that, in addition to this, there is probably some organic change in these arterioles, and that, if this organic lesion becomes extreme, areas of the skin of the legs or of the digits may become gangrenous.



intimal proliferation in fairly large veins in Case 1 and this may have been a factor in the development and persistence of the ulcers.

*Symptoms.*—Persistent livedo reticularis may exist as a benign disorder for many years, with minimal or no discomfort. Most of our patients complained of more or less coldness and occasional numbness of their legs, even at average room temperature, and of accentuation of these symptoms with a decrease in environmental temperature. A few patients stated that there was also rather diffuse pain or aching, particularly in the region of the ankles, during cold weather. However, the only serious symptoms seemed to be in those cases in which ulceration and gangrene occurred. In these cases pain was quite severe and persistent. In Case 1, in which there were peripheral neuritis and extensive recurring ulceration which was refractory to treatment, amputation of both legs was ultimately necessary because of the severe pain and nonhealing of the ulcers.

*Diagnosis.*—If one regards livedo reticularis as a clinical entity, the diagnosis can be readily made from the appearance of the extremities. The persistence of the discoloration, its blotchy or reticular distribution, and the extent of the involvement (lower extremities to the knees or above, possibly arms and trunk also) distinguish livedo reticularis from Raynaud's phenomenon and acrocyanosis. It can be distinguished from thromboangiitis obliterans by the lack of evidence of occlusion of the larger arteries (normal pulsations), and by the fact that the livid discoloration appears in the legs, which, in our experience, has not been observed in cases of thromboangiitis obliterans. Although definite inflammatory changes in the arterioles have been noted in most of the cases in which biopsies have been made, they are not similar to the changes which occur in thromboangiitis obliterans. In contradistinction, thrombosis or complete occlusion of the lumen is unusual, and the medium-sized and large arteries are not affected. The lesions do not show the medial necrosis which is seen in periarteritis nodosa, and the course of the disease is benign as compared with periarteritis nodosa. Sclerodermatous changes in the skin were not observed in any of our cases, nor have they been described in the literature in association with livedo reticularis.

*Treatment.*—Since the symptoms are mild in the uncomplicated cases, and the condition may endure for a number of years without evidence of progression, it is doubtful whether any therapy is necessary, other than protection of the body as a whole, and particularly the areas involved, from exposure to cold. Inasmuch as the true cause of the condition is not known, there can be no rational therapy at present. However, patients with livedo reticularis may also have tuberculosis or syphilis, and, if either of these conditions is present, it should receive appropriate treatment. Also, the possibility of poisoning by lead or

arsenic should be considered, and treatment instituted if indicated. In those cases in which there is ulceration or gangrene, a period of rest in bed while these lesions are active and the use of medical and physical vasodilating procedures seem advisable.

As has been stated, lumbar sympathetic ganglionectomy was performed in three of our cases (Cases 1, 2, and 5). In the two cases (Cases 2 and 5) in which there was gangrene of the toes, the livedo reticularis itself almost completely disappeared after sympathectomy; the skin remained warm; symptoms of coldness and aching were relieved, and no further gangrene has developed. The observation period has been three years in Case 2 and one year in Case 5. In Case 1, in which the livedo was intense and widespread and there were extensive, painful ulceration of the legs and arterial occlusion in the toes, lumbar sympathetic ganglionectomy was followed by healing of the ulcers and no recurrence for a year. Also, no further arterial occlusion in the toes developed in this case. However, after that time the ulceration recurred and was progressive, eventually necessitating amputation of both legs. In the sympathectomized parts (below the knees) the livedo was only slightly less prominent, but the discolored areas remained pink rather than blue. In this case a rather severe degree of livedo reticularis of the arms also developed, and a cervicodorsal sympathectomy was done; this had only a slight influence on the livid areas, but relieved the aching and coldness in the hands which accompanied the livedo.

#### SUMMARY

We have reported a series of thirteen cases of peripheral vascular disease affecting chiefly the legs and feet which seems to us to be best classified under the term "livedo reticularis," as described in the literature. The clinical manifestations differ distinctly from those of Raynaud's disease, acrocyanosis, and thromboangiitis obliterans. These patients did not have evidence of tuberculosis or syphilis, and the circulatory disturbance developed during adult life. The etiology in our cases is not known.

The available data in our cases and others indicate that in livedo reticularis there are usually organic changes in the arterioles of the skin, with chronic vasospasm, which result in regional atony and dilatation of capillaries and slowing of the blood flow. The condition may be complicated by ulceration of the legs and superficial gangrene of the toes. Lumbar sympathetic ganglionectomy resulted in definite improvement in circulation and prevention of further attacks of gangrene in two of our cases and was unsuccessful in one case. It is our opinion that sympathectomy is a justifiable procedure in cases of livedo reticularis in which (1) no definite etiological factor can be found, and (2) superficial gangrene is present.



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## DISCUSSION

DR. A. WILBUR DURYEE, New York.—We have seen a number of these cases in and around New York. There is a question I should like to ask Dr. Barker. In taking the history in these cases, did he inquire whether the extremities had been exposed to excessive heat? We find that most of our patients have either stood in front of very hot fires, or have been exposed to excessive sunlight on the beach. You will note that the pictures Dr. Barker showed were mostly of the anterior surfaces of the lower legs and the exposed surfaces of the arms. In most of our cases the lesions were most marked in these localities, and, although it is far from proved, I think that one possible etiological factor is destruction of some of the vessels by excessive heat.

In extensively burned areas one often sees mottling which is very similar to that in the cases which he presented.

I would also like to ask Dr. Barker whether he tried mecholyl iontophoresis as a form of therapy. Many of these patients come to us because of cosmetic faults, and I wonder whether mecholyl iontophoresis had any beneficial effect on the livid appearance.

Two patients whom we have followed have marked hypothyroidism and have responded fairly well to adequate doses of thyroid.

DR. NELSON W. BARKER, Rochester, Minn.—The literature contains descriptions of livedo reticularis which developed after exposure to heat, as was mentioned by Dr. Duryee. None of our patients gave a history of exposure to unusual heat, nor did they work in environments in which this might occur. Also, the livedo was as prominent on the posterior surfaces of the legs and on the soles of the feet as it was on the anterior surfaces of the legs, where exposure to heat might be more likely to occur. We did not treat any of our patients with mecholyl administered by iontophoresis. The injections of mecholyl were used only to obtain information regarding the physiologic disturbance, and not as a therapeutic measure. The suggestion that mecholyl administered by iontophoresis be used in treatment is a good one, although the chronicity of the disease might limit its effectiveness, except during the periods of painful ulceration and gangrene. Livedo reticularis has been described in association with both hypothyroidism and hyperthyroidism. It is doubtful whether there is any etiological relationship between either of these two conditions and livedo reticularis.

# OBSERVATIONS ON THE PATHOLOGIC EFFECTS OF THIOCYANATE

## AN EXPERIMENTAL STUDY

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### INTRODUCTION

**A**SIDE from any alteration of symptoms or blood pressure of patients with hypertension, the effect of the administration of therapeutic doses of the salts of thiocyanate<sup>1, 2</sup> has consisted chiefly of reduction in the erythrocyte count, hematocrit value, total serum proteins, and plasma cholesterol, and an increase in the erythrocyte sedimentation rate.<sup>3, 21, 22</sup> Not all of these changes occur regularly, but they may be associated with a 1- to 3-month therapeutic blood concentration of 8 to 12 mg. per 100 c.c. Toxic concentrations (15 to 20 mg.) usually bring about or exaggerate these changes.<sup>2</sup> Therefore, toxic doses of the thiocyanate salts were given to dogs for long periods of time in order to extend our knowledge of the pharmacology and toxicology of these drugs.

### LITERATURE

No attempt will be made to review the clinical aspects, except to state that the discussion of the "empirical use"<sup>4</sup> of the thiocyanates has continued<sup>1, 5-7</sup> without a good understanding of their pharmacology and toxicology.<sup>1, 2, 5, 8-15 et al.</sup> From the experimental standpoint, reference may be made to the recent review and excellent experimental study of Anderson and Chen.<sup>16</sup>

### METHODS

The laboratory procedures which were used include the following: For the determination of blood cholesterol, the method of Bloor<sup>17</sup> was employed; the determination of serum proteins was done by a method adapted from combined techniques of Howe<sup>18</sup>, Wu<sup>19</sup>, and Koch and McMeekin<sup>20</sup>; a modification of Schreiber's technique<sup>1</sup> for the determination of blood thiocyanate was used. Frequent duplicate analyses by more than one technician were made as a check upon the determination of total proteins and cholesterol.

### EXPERIMENTAL OBSERVATIONS ON BLOOD CHOLESTEROL, TOTAL PROTEINS, ERYTHROCYTE COUNT, AND HEMATOCRIT READING

For the purpose of this experiment, twelve normal dogs were given potassium thiocyanate orally in 5-grain (0.3 Gm.) doses. Observation of the blood thiocyanate content at frequent intervals was the guide to

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daily dosage for the maintenance of toxicosis. The results were tabulated individually for each animal, and the actual values for the blood thiocyanate and the particular constituent being studied are shown side by side.

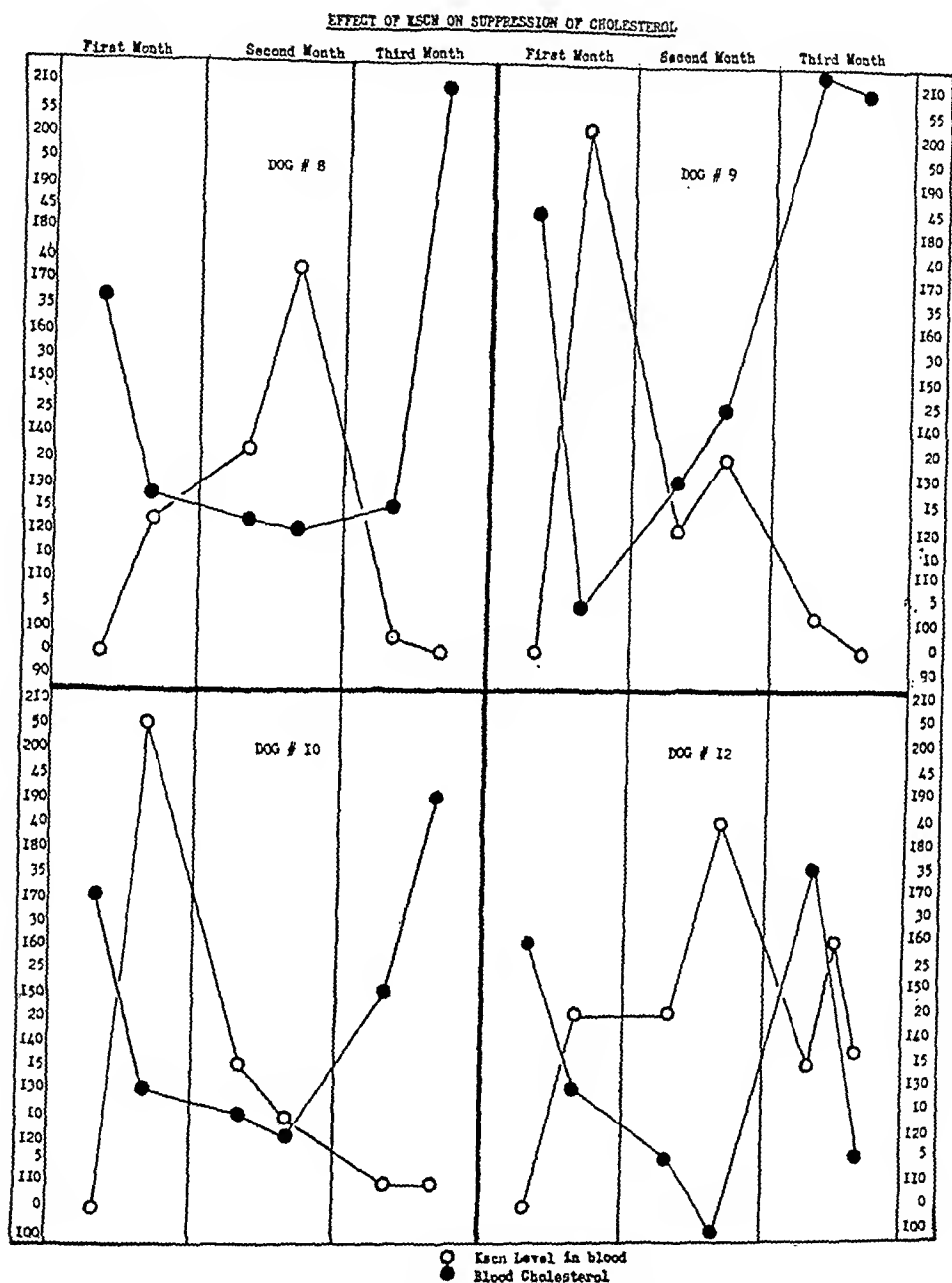


Fig. 1.—Showing the relationship of the levels of blood thiocyanate (mg. %) and plasma cholesterol (mg. %) in Dogs 8, 9, 10, and 12. KSCN = potassium thiocyanate (cf. Table I).

For the study of the effect of thiocyanate upon blood cholesterol values (Table I and Fig. 1), a checked duplicate control reading was recorded. It will be noted that in each case a variable but significant fall in blood cholesterol occurred very promptly upon administration of the thiocyanate. It is noteworthy that the fall was abrupt at first, although the actual quantity of thiocyanate in the blood may have been small. In

each case, the subsequent cholesterol level was variable, but a rough parallel between elevation of blood thiocyanate and reduction of blood cholesterol values was apparent. After the original, prompt diminution in cholesterol, the subsequent decline was considerably slower; that is, the gradient of the fall was prolonged over several weeks after a peak in blood thiocyanate value had been reached.

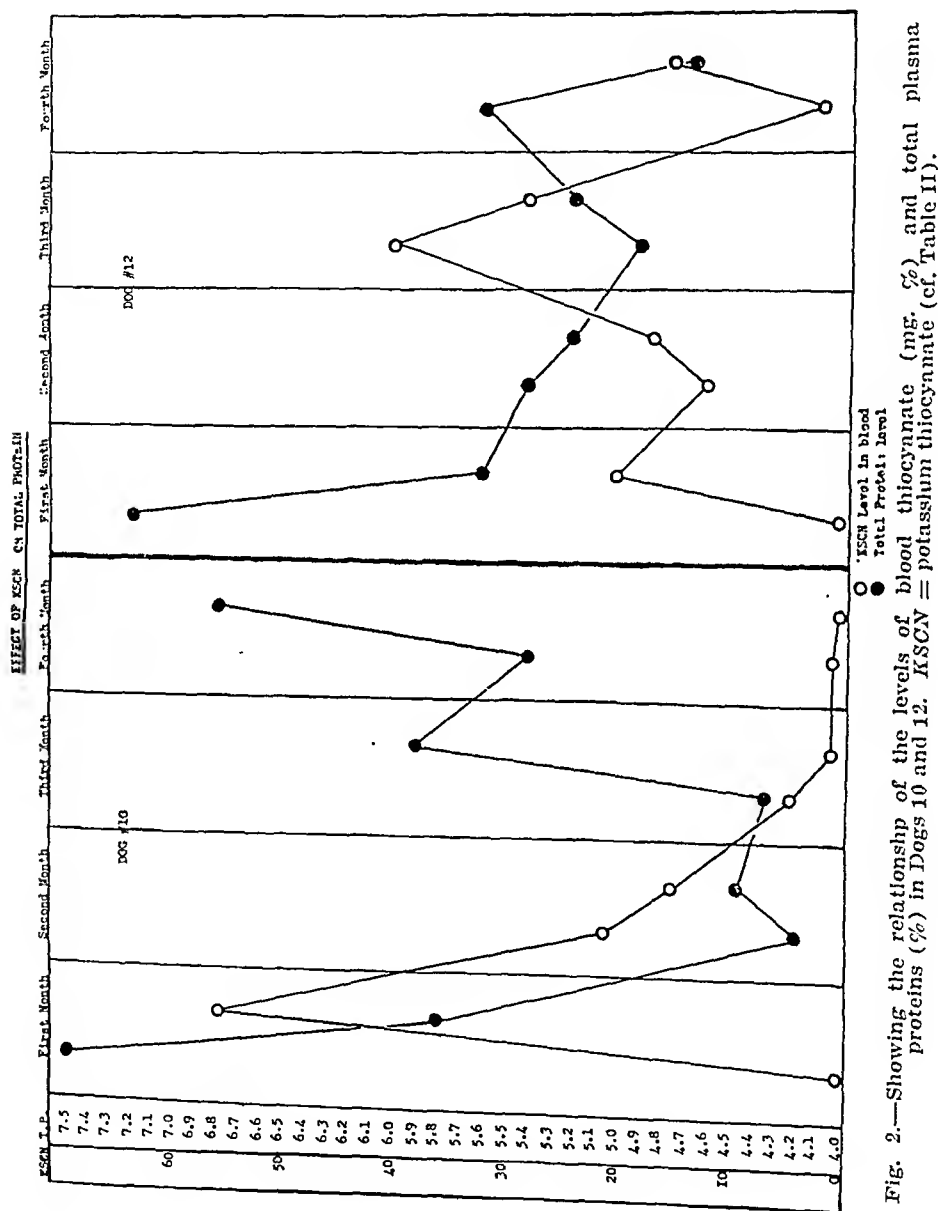


Fig. 2.—Showing the relationship of the levels of blood thiocyanate (mg. %) and total plasma proteins (%) in Dogs 10 and 12. KSCN = potassium thiocyanate (cf. Table II).

There is a tendency for cholesterol values to rise far beyond the original control content when the blood thiocyanate level is permitted to fall (see Table I and Fig. 1).

The response of the blood proteins (Table II and Fig. 2) to thiocyanate is characterized by a prompt initial fall, and by a lag in recovery as the blood thiocyanate level declines. A fall, after a distinct sec-

TABLE  
FLUCTUATIONS OF BLOOD CHOLESTEROL (MG. %) IN

DOG	BLOOD	DURATION OF THIOCYANATE											
		0	1	2	3	4	5	6	7	8	9	10	11
4	Sen		5.6			30.3	16		20	13.4	22.2	20.2	14.8
	Chol	172				121			164				232
5	Sen				20	60.2							
	Chol	166				87.5							
8	Sen			3.46		15.7	23	38.4	0	0	0	0	
	Chol	167				126			123	116		125	
9	Sen		56	21	0	15.4	20	4.45	0	0	0		
	Chol	194			114		135	147		227	223		
10	Sen					51.5	15.6	8.25	0	0	0		
	Chol	166			131		126	123		149	195		
12	Sen			20	12.4			17	41	16.7	22.2	28.6	
	Chol	160		130				116	89	179		136	
14	Sen					tr	0	17	26.9	3.8	9.5	20.6	
	Chol	150					110	102	80.5	151	186	154	
17	Sen		27.5		0		19.4	27	21.6	10.8	33.4		
	Chol	166	125		142		125	147	167	189	222		
18	Sen		13.9	8.0	75.2		tr	2.36	23			0	
	Chol	169	147	122	117	89	248	250	158	214	348	321	
19	Sen		20	12.2	17.9	37			0				
	Chol	180	87	86.3	93.3	96	143	205	150				

Sen = blood thiocyanate; Chol = plasma cholesterol (cf. Fig. 1.)

TABLE  
FLUCTUATIONS OF TOTAL PLASMA PROTEINS (%) IN

DOG	BLOOD	DURATION OF THIOCYANATE											
		0	1	2	3	4	5	6	7	8	9	10	11
4	Sen		5.6			30.3	16		20	13.4	22.2	20.2	14.8
	T. P.	5.5				5.02			5.7		4.89		4.48
5	Sen				20	6.02							
	T. P.	7.0				5.81							
8	Sen			3.46		15.7	23	38.4	0	0	0	0	
	T. P.	7.24		6.13				5.84	6.7	5.84		5.25	
9	Sen		56	21	0	15.4	20	4.45	0	0	0		
	T. P.	7.7		5.8		4.7	4.45	4.36		5.5	5.96	5.4	
10	Sen					5.15	15.6	8.25	0	0	0		
	T. P.	6.6			5.51	4.48	5.8	5.65		5.58	6.6	5.12	
12	Sen			20	12.4			17	41	16.7	22.2	28.6	
	T. P.	7.2		6.0	5.4			5.2	6.5	4.87		5.03	
14	Sen					tr	0	17	26.9	3.8	9.5	20.6	
	T. P.	7.0				5.4	7.8	5.28	5.51	5.48	6.7		
17	Sen		27.5		0		19.4	27	21.6	10.8	33.4		
	T. P.	6.5	6.8		6.5		5.22	4.2		6.5	5.18		
18	Sen		13.9	8.0	75.2		tr	2.36	23			0	
	T. P.	6.9	5.49	5.09	4.29	3.93	5.6	6.9	5.58	6.13	5.65	5.4	
19	Sen		20	12.2	17.9	37			0				
	T. P.	6.5	5.21	5.15	4.3	4.04	6.0	6.45	6.05				

Sen = blood thiocyanate; T. P. = total plasma proteins (cf. Fig. 2).

I.

RELATION TO BLOOD CONTENT OF THIOCYANATE (MG. %)

ADMINISTRATION IN WEEKS															
12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
208															
208															
0		15.5													
121		104													
0	15		33.4	28.6	0			3.2	7.6	14.1	14	35		24.4	tr
147	104		138	119	152			158		147	147	166		161	130
															/

II

RELATION TO BLOOD CONTENT OF THIOCYANATE (MG. %)

ADMINISTRATION IN WEEKS													
12	13	14	15	16	17	18	19	20	21	22	23	24	26
5.80	5.58												
7.0													
0		15.5											
5.7		4.73											
0	15		33.4	28.6	0			3.2	7.6	14.1	14	35	24.4
6.7	4.73		5.31		6.22			7.24		6.05	6.35	4.46	5.83

TABLE  
DECLINE OF HEMATOCRIT VALUE AND ERYTHROCYTE COUNT

DOG	BLOOD	DURATION OF THIOCYANATE											
		0	1	2	3	4	5	6	7	8	9	10	11
1	Sen	0			22.6	9.8	16.6	10.7					
	Hem	37.6			41	39	39	36					
	RBC	5.3							34.8				
2	Sen	0	13.7										
	Hem	61	42.5		50	44	22.8						
	RBC	6.3	6.03		4.8								
4	Sen		5.6			30.3	16		20	13.4	22.2	20.2	14.8
	Hem	37	44	41		36.6	24		19.5	20	24		22
	RBC	5.65				5.68	4.37		4.26				4.1
8	Sen			3.46		15.7	23	38.4	0	0	0	0	
	Hem	55	55	39		40	31	35	32	30	32	36	37
	RBC	5.43	5.5			4.25		5.04				4.46	
9	Sen		56	21	0	15.4	20	4.45	0	0	0		
	Hem	47	45	33	39	25	32	11.5		18.1	37		
	RBC	5.95			5.28	2.97					2.27		
10	Sen					51.5	15.6	8.25	0	0	0		
	Hem	46			40	40	37			30	37		
	RBC				5.4	5.4				5.0			
14	Sen					tr	0	17	26.9	3.8	9.5	20.6	
	Hem	51				51							
	RBC	6.3											
17	Sen		27.5		0		19.4	27	21.6	10.8	33.4		
	Hem	51	48		45		45	35	36	30	18		
	RBC	6.3									3.09		
18	Sen		13.9	8.0	75.2			0					
	Hem	54	44		38	27		33					
	RBC	8.14	5.34		5.9		5.5	5.7					
19	Sen		20	12.2	17.9	37							
	Hem	57	53		44		27						
	RBC	8.26		7.35	6.87	5.45	3.97						

Sen = blood thiocyanate; Hem = hematocrit percentage; RBC = Red blood corpuscles in

ondary rise, in total protein value, even though the blood was entirely clear of sulfoeyanate, occurred, and no tendency toward a late rise to levels exceeding this original control value was observed. When the blood proteins were diminished, either the albumin or the globulin fraction was more profoundly affected, or both were equally reduced. Clinically, we have observed a diminution of the globulin portion with therapeutic doses of the drug. Experimentally, in these dogs, toxic doses of the drug produced a proportionate reduction of both the albumin and globulin portions.

Turning our attention to the anemia which developed in our animals, we note that Taubman and Heilborn<sup>11</sup> found that fourteen of fifteen guinea pigs which were given two doses of 0.2 Gm. per kilogram of potassium thiocyanate showed a 25 per cent fall in both hemoglobin and erythrocytes. With smaller doses, given orally over longer periods of

## III

IN RELATION TO BLOOD THIOCYANATE LEVEL (MG. %)

ADMINISTRATION IN WEEKS															
12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
0															
42															
0	15	33.4	28.6	0				3.2	7.6	14.1	14	35		24.4	
39	41	31	31	30					4.1		30				
5.39		4.62									3.8				

millions (cf. Fig. 3).

time, the hemoglobin and erythrocyte count could be reduced even lower before convulsions ensued.

The fall in the erythrocyte count and the hematocrit value in our series of dogs was striking (Table III and Fig. 3). The gradient in most cases was very gradual. In several instances there was a brief initial rise in the hematocrit value before the fall commenced. The progress of the reduction of the erythrocyte count and hematocrit value was slow and prolonged, persisting at least beyond the limits of these experiments and long after the thiocyanate had been stopped. Following the cessation of administration of the drug there was a slowing of the fall in the erythrocyte count, or an actual arrest of the fall. The hematocrit value, which showed a much wider response, tended to stabilize more quickly after the blood was cleared of thiocyanate. In some animals a slight tendency toward a rise to original levels was indicated.



In attempting to classify this type of anemia, we find that there was a definite fall in hemoglobin, hematocrit reading, and erythrocyte count. The color index and volume index ran somewhat less than 0.8. The Price-Jones curves showed a tendency to shift to the left. The differential leucocyte count was normal. The polymorphonuclear leucocytes and other cells of the granulocytic series were normal despite the intoxication. The reticulocyte count was normal. There was no icterus or hemosiderosis. No change occurred in the fragility of the cells.

SULPHOCYANATE EFFECT ON HEMATOCRIT, RED AND WHITE CELL COUNTS.

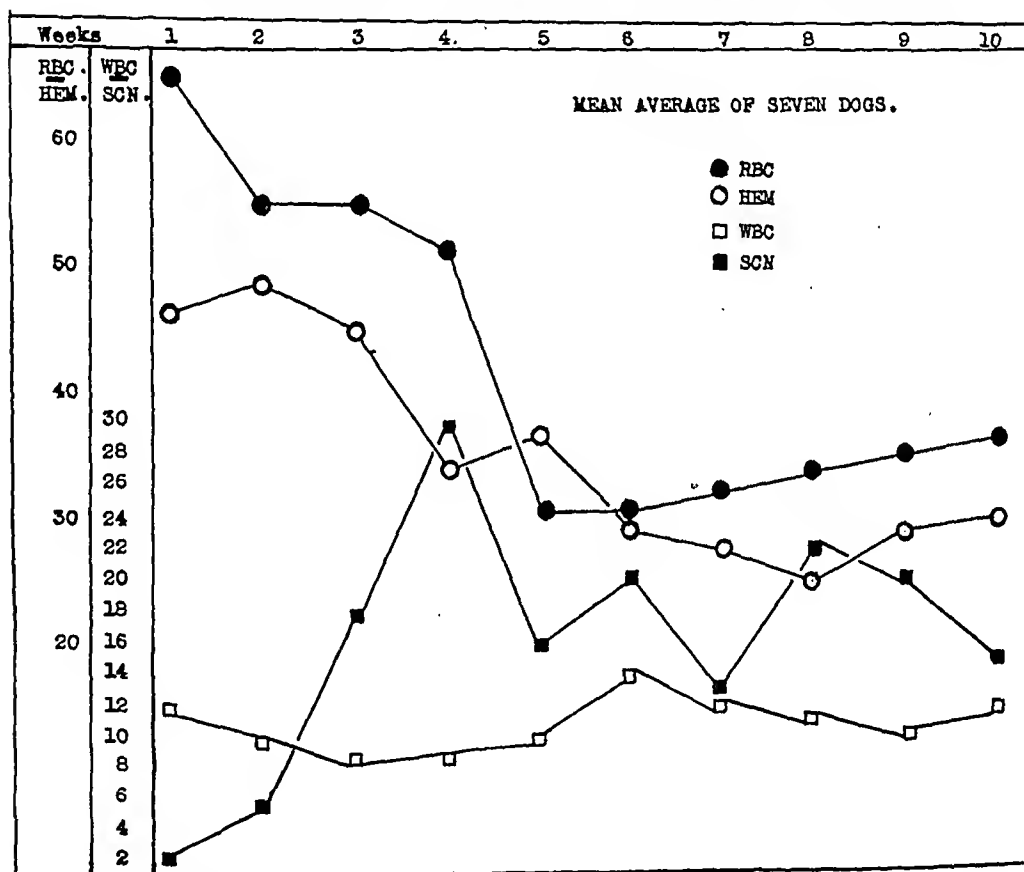


Fig. 3.—Showing the relationship between the hematocrit and erythrocyte levels and the blood thiocyanate curve. The leucocyte level remains essentially unchanged. This graph is a composite of the curves taken from readings on seven dogs, and the curves represent the mean averages. *RBC* = red blood corpuscles in hundred thousands; *HEM* = hematocrit percentage; *WBC* = white blood corpuscles in thousands; *SCN* = blood thiocyanate in milligrams per cent (cf. Table III).

#### TISSUE STUDIES

It has been shown that thiocyanates permeate all tissues in essentially the same concentration.<sup>2, 13</sup> Hence, the tissue content cannot be presented as evidence favoring one organ or another as the site of their action. Grossly, examination of the bodies of animals and men to whom thiocyanates have been given yields no clues to the action of the drug. However, in our experimental animals, bone marrow sections (biopsy from the sternum, rib, and femur) revealed a relatively acellular bone marrow. In the least severely intoxicated animals, the normal matrix

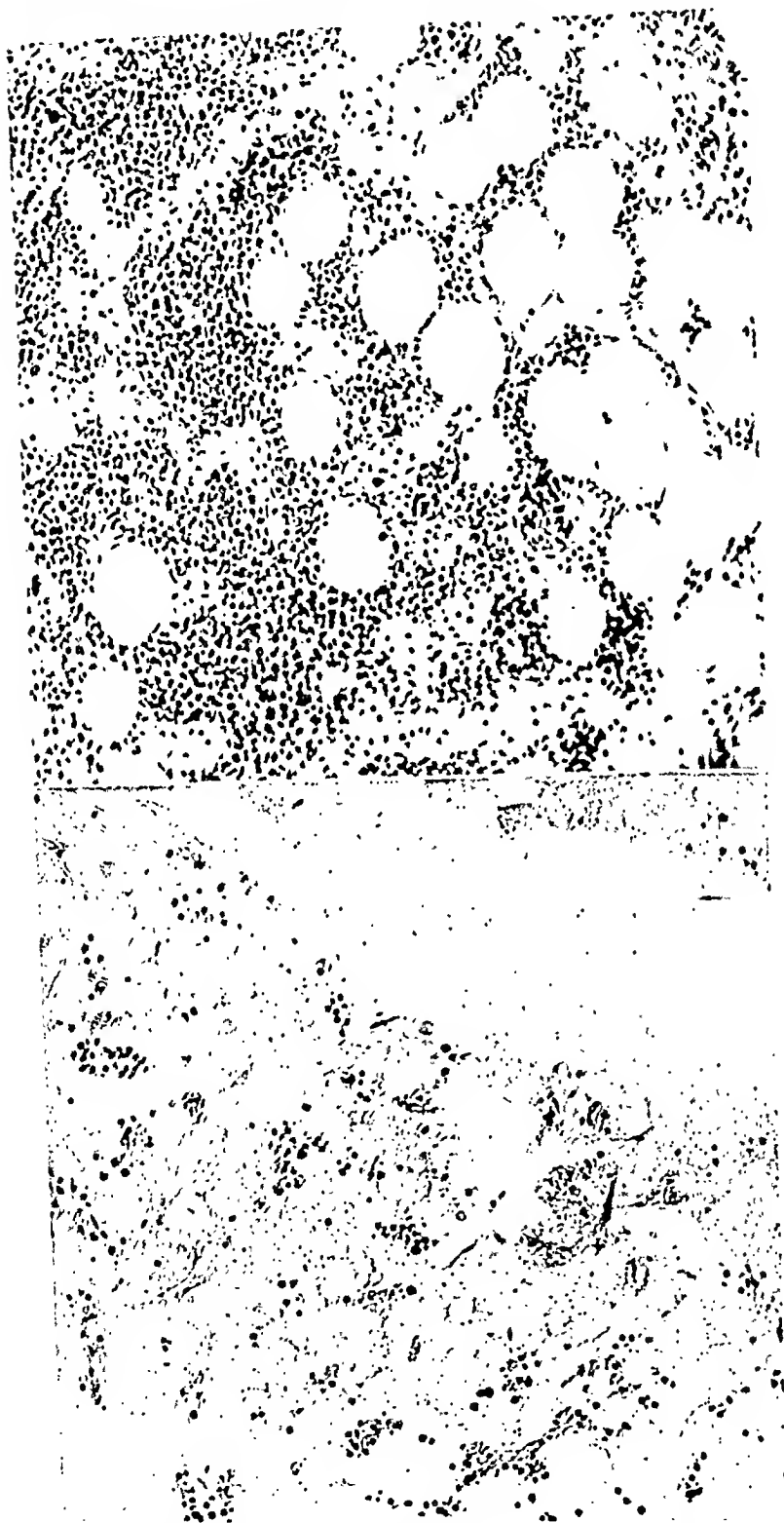


Fig. 4.—Photomicrographs ( $\times 250$ ) showing, top, the normal bone marrow of a dog, for comparison with the bone marrow of one of the dogs that had been subjected to prolonged intoxication with thiocyanates. The degeneration in the field shown in the bottom photograph is striking and is wholly typical of the changes observed in the marrow of all of the dogs in the series.

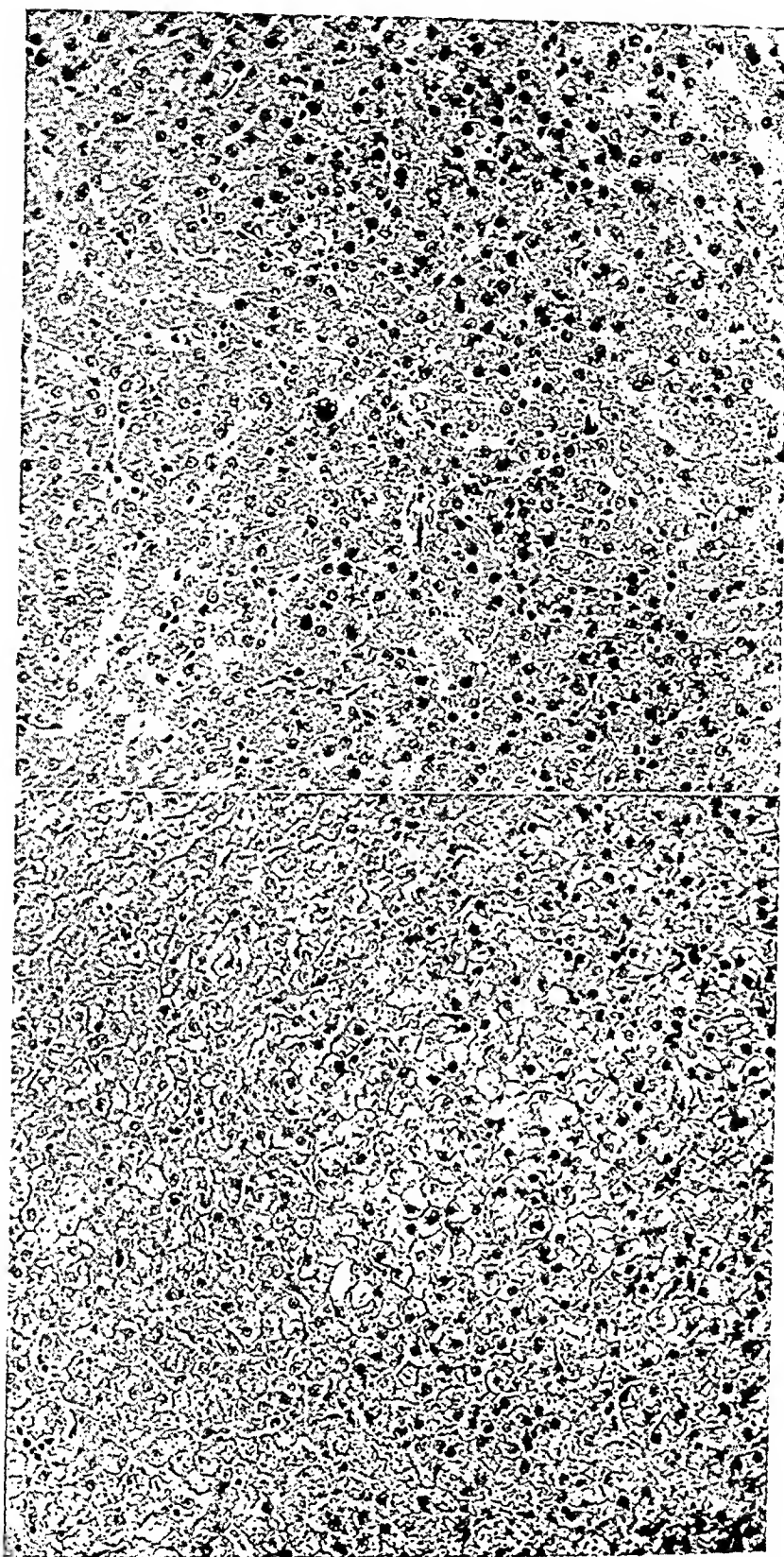


Fig. 5.—Photomicrographs ( $\times 250$ ) of the liver of Dog 14. The top photograph shows essentially normal liver tissue which was obtained before the experiment. The bottom photograph shows the degenerative changes which have occurred in the liver of the same dog after prolonged intoxication with thiocyanate. These were observed in all of the dogs of the series.

was replaced by fat. As toxicity became more severe, the fatty marrow was replaced by a clear, light, eosin-staining gelatinous material; the picture was not unlike that of benzol poisoning (see Fig. 4).

Biopsies of the livers were taken before, during, and after the administration of the drug. The livers of dogs which were fed excessive doses of inorganic sulfoeyanate salts showed intracellular fatty vacuolization of marked degree (see Fig. 5). The changes were very diffuse, involving the parenchymal cells, and there was practically no tendency toward regeneration or compensatory hyperplasia during the period of study. The icteric index of the animals was never increased. No comparable changes have ever appeared in the tissues of man. However, it may be possible that functional hepatic changes not demonstrable by anatomic methods may occur, as suggested by the alterations in blood cholesterol and total serum protein. Routine examination of the myocardium, kidneys, spleen, pancreas, lungs, and thyroid gland showed no gross or microscopic alteration.

Anatomic changes in the adrenal glands were entirely lacking. Our analyses of human and animal tissue for thiocyanate content did not show that there is a greater quantity stored in this organ than in others. Chemical analyses of the blood, with special reference to sugar metabolism, sodium, potassium, and chloride, also failed to disclose evidence of interference with adrenal function. For these reasons we are unable to support the impression of Healy<sup>12</sup> that "hypoadrenia" may be the principal feature of the toxicology of the thiocyanates.

#### DISCUSSION

From the standpoint of the work which we have presented here, two points must be made clear. First, many instances of marked lowering of blood pressure in hypertensive patients are observed long before any of these changes in total protein, cholesterol, or formed elements take place. This suggests that a vasodilating effect occurs first, and that the hemie responses, *if they occur at all*, only mirror other systemic alterations. Second, the properly controlled human subjects with hypertension who have been referred to were given only a sufficient quantity of the thiocyanates to maintain blood concentrations that were considered safe (8 to 14 mg. per cent), whereas very toxic amounts (20 to 60 mg. per cent) were given to these normal experimental animals.

#### CONCLUSIONS

Toxic doses of thiocyanates, when given to normal animals for long periods of time, produced a marked microcytic anemia and a diminution of blood cholesterol and total serum proteins. Tissue studies of these animals showed significant liver and bone marrow changes.

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# QUANTITATIVE CHANGES IN THE CAPILLARY-MUSCLE RELATIONSHIP IN HUMAN HEARTS DURING NORMAL GROWTH AND HYPERTROPHY\*†

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IT IS generally believed that normal growth of the human heart is accompanied by an increase in the diameter and length of the individual muscle fibers, and that when growth is completed, the fibers remain constant in size. In other words, one of the integral parts of growth is an increase in the diameter of the muscle fibers. It is also well known that, as a result of certain pathologic conditions, the heart may undergo hypertrophy, during which the diameter of the cardiac muscle fibers may increase well beyond the limits reached during normal growth. Relatively little is on record, however, of the concomitant changes that occur in the myocardial capillaries during normal growth and hypertrophy of the human heart.

Horvath<sup>2</sup> and Albrecht<sup>3</sup> were among the first to associate cardiac failure with an hypertrophy of the muscle fibers, but the work of Goldenburg,<sup>4</sup> Tangl,<sup>5</sup> Dehio,<sup>6</sup> Stadler,<sup>7</sup> and Letulle<sup>8</sup> established the fact that gross hypertrophy of the heart is the result of enlargement of the individual muscle fibers. Karsner, Saphir, and Todd<sup>9</sup> observed an increase in the fiber diameters in an hypertrophied heart and a decrease in an atrophied heart.

In 1928, Wearn,<sup>10</sup> following Krogh's<sup>11</sup> quantification of capillaries in skeletal muscle, devised a method for counting the capillaries in human and animal hearts. Their counts were high, however, due to shrinkage during fixation of the blocks of muscle. Vannotti,<sup>12</sup> using the method of Wearn, found an initial increase, followed by a decrease, in twelve dogs' hearts during hypertrophy. Petren, Sylven, and co-workers<sup>13-16</sup> and Vannotti<sup>17</sup> have used the benzidine stain of Sjostrand<sup>18</sup> for the counting of myocardial capillaries in guinea pigs and have claimed that during growth, during pregnancy, and following exercise, the capillaries increased in number. The benzidine method stains erythrocytes and not the capillary wall,

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\*The experiments reported in this paper have been in progress for several years. Dr. and Mrs. R. A. Shipley and Dr. J. J. Badal took part in some of the earlier experiments. Dr. J. T. Roberts has collaborated during the past four years. (J. T. W.)

†Some of the earlier results of the work were presented before the Society for Experimental Biology and Medicine (1), and before the Association of American Physicians (2).

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so, when used for the demonstration of capillaries, it will show only those capillaries which contain erythrocytes at the level at which the capillary is cut. It is extremely rare, in our experience, to find a heart in which the capillaries are evenly filled with red blood cells. Indeed, in sections showing myocardial capillaries cut longitudinally, it is common experience to find long segments of many of the capillaries without a single red cell in them. In sections cut through such areas of the capillaries, the vessel walls would not be shown with the benzidine stain. For this reason, the method in our hands has proved wholly unreliable for the quantification of capillaries.

Shipley, Shipley, and Wearn<sup>19</sup> determined the fiber-capillary ratio, concentration of capillaries, and fiber diameters in fifteen normal and eighteen hypertrophied rabbit hearts. They showed that during growth the myocardial capillaries increased in number to keep pace with the increasing muscle mass. During hypertrophy, however, the fibers increased in diameter, thus causing an increase in the muscle mass, without a corresponding increase in capillaries. As a result of the hypertrophy, therefore, each capillary had a considerably greater mass of muscle to which it supplied blood. Christian<sup>20</sup> has long taught that this change may play a definite role in the failure of the hypertrophied human heart.

#### MATERIAL

The human hearts used for injection and study in this work were taken consecutively as they came to necropsy, whenever they could be obtained soon enough post mortem to permit successful injection of the capillaries. There was a fairly even distribution as to sex, color, and age in the normal and abnormal groups. Seventy-seven hearts collected over several years' time were used in this study. Eight of these were normal hearts from children of various ages; twenty-six were hearts of normal size from adults, forty were hypertrophied hearts of adults, and three were atrophied hearts of adults who died of wasting diseases.

#### TECHNICAL PROCEDURES

These hearts were obtained usually within an hour post mortem. After removing the fluid and clotted blood from the chambers, the weight was recorded. Cannulae were tied into the coronary arteries and connected with the injection apparatus. By means of these, the coronary arteries were perfused with oxygenated Locke-Rosenheim solution at a temperature of 37° C. and at a pressure of 80 mm. of mercury. When rhythmical contractions of the chamber were well established, injection of the capillaries was carried out in the manner previously described by Shipley, Shipley, and Wearn.<sup>19</sup> Twelve hearts obtained four to ten hours post mortem were successfully injected by use of the method described by Wearn, Bromer, and Zschiesche,<sup>21</sup> with the exception that 2 per cent Chicago blue in 20 per cent gelatin was substituted for the India ink. The injection pressure used in this latter group was 180 mm. of mercury.

Blocks of tissue were removed for study from each ventricle, and, as nearly as possible, from identical sites in each instance.

In preparing sections of the heart for study, the greatest care was used to prevent shrinkage of the tissue. The method used for imbedding in gelatin and mounting the frozen sections has been described previously.<sup>19</sup> The blocks of fresh tissue

and the mounted sections cut from them were carefully measured to control any shrinkage factor, if present. The freshly mounted sections were counted immediately.

All counts and measurements were made with oil immersion objectives and cross-ruled ocular micrometers, which covered an area of tissue varying, according to the microscope used, from 3,250 to 3,500 square micra. Calibration of these instruments was carried out frequently throughout the study. The capillaries and fibers were counted with the aid of the ruled micrometer ocular in the manner that one counts red blood cells in a ruled counting chamber. Each observer measured in each section all of the first twenty muscle fibers which touched a single point of the ruled ocular micrometer as the slide was moved laterally by means of the mechanical stage. Since many cardiac muscle fibers are elliptical in cross section, both the long and short diameters were measured routinely. These two measurements were averaged separately and then an average of the two was computed for the mean fiber diameter. In making the counts and measurements of capillaries and muscle fibers, microscopic fields with large septa of connective tissue, large arteries and veins, and artificial tears in the section were avoided. Counts and measurements were made only in those fields in which the capillaries and muscle fibers were cut in perfect cross section, and in which the capillaries were completely injected. The identity of the heart on which counts and measurements were being made was unknown to the observer until the observations on that heart were completed. Counts and measurements were made independently on most hearts by three observers, and by at least two observers in all instances.

In addition to the counts of capillaries and the measurements of muscle fibers, the area of connective tissue in each field was estimated by means of the ocular micrometer.

Counts and measurements were made in eight fields of each section by each observer, and the final average was calculated from all observations. The number of observations on each heart was sufficiently large to reduce the probable error of the mean to a point well below the limits dictated by the accepted methods of statistics. Many forms of statistical analysis were tried, but for the sake of brevity, only the arithmetic means, with their probable errors, will be cited.\*

#### NORMAL HEARTS OF CHILDREN

The eight patients in the infants' and children's group ranged in age from slight prematurity to 16 years. All the hearts in this group were normal in every respect, including weight. The ratios of heart weight to body weight were higher than those of the adult group, which is in keeping with the standards generally accepted for children. The heart weights ranged from 13 to 237 Gm., with a mean of 90.8 ( $\pm 19.0$ ) Gm. The average fiber diameter for the hearts in this group ranged from 6.4 to 11.2  $\mu$ , with the mean being 8.96 ( $\pm 0.38$ )  $\mu$ . It is recognized that this is a small group of hearts and that the ages of the children were scattered. There are no hearts from children between the ages of 1 and 8 years. The mean figures for the group, therefore, are not necessarily representative. Table I shows the individual variation.

The concentration of capillaries in the eight children's hearts ranged from 3,230 to 4,513 capillaries per square millimeter, the mean being

\*We are indebted to Prof. J. R. Musselman of the Department of Mathematics of Western Reserve University, who reviewed and criticized our mathematical treatment of these data.



3,744 ( $\pm 122$ ). This average and degree of dispersion showed that the concentration of capillaries in the growing child's heart, regardless of age or of muscle fiber size, remains approximately constant. Thus, the capillary concentration is fairly constant from the time of birth throughout the period of physiologic growth.

TABLE I  
NORMAL CHILDREN'S HEARTS

NO.	HEART WEIGHT (GM.)	AGE	HEART WEIGHT-BODY WEIGHT RATIO	FIBER DIAMETER ( $\mu$ )	CAPILLARIES PER SQ. MM.	FIBER-CAPILLARY RATIO
H85L	13	-3 mo.	0.00655	6.4	3,365	5.90
62	18	3 mo.	0.00927	8.4	4,458	3.81
34	20	3 wk.	0.00690	7.4	4,513	4.04
77	48	10 mo.	0.00768	8.7	3,230	3.30
73	110	8 yr.	0.00478	9.5	3,558	2.10
88	140	11 yr.	0.00400	9.3	4,028	2.04
20	140	11 yr.	0.00353	10.8	3,395	2.39
76	237	16 yr.	0.01096	11.2	3,401	2.25
Average	90.75	5.91 yr.	0.00671	8.96	3,743.5	3.23

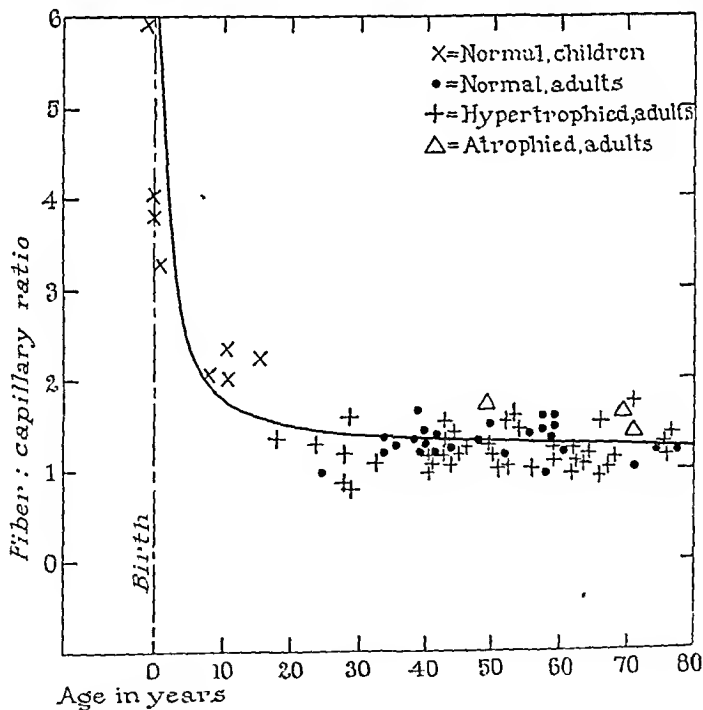


Chart 1.—Changes in the fiber-capillary ratio during growth and hypertrophy.

On the other hand, the ratio of the number of muscle fibers to the number of capillaries per square millimeter—the “FC ratio”—showed a very significant change during the period of normal growth. From the time of birth the FC ratio was found to decrease during the period of physiologic growth until the ratio approached one (1.34), where it remained throughout normal adult life, as will be

shown later. This decrease in the FC ratio with increasing age occurred in accord with an hyperbolic curve, a type of change frequently encountered in studies of growth phenomena (see Chart 1). Despite the small number of children's hearts, this curve is the same as that found for the growing rabbit hearts.<sup>19</sup> In the heart of a premature infant (three months premature) there were 5.90 muscle fibers to each capillary. The fibers in this heart were very small and the capillary concentration was within normal limits (Fig. 1).

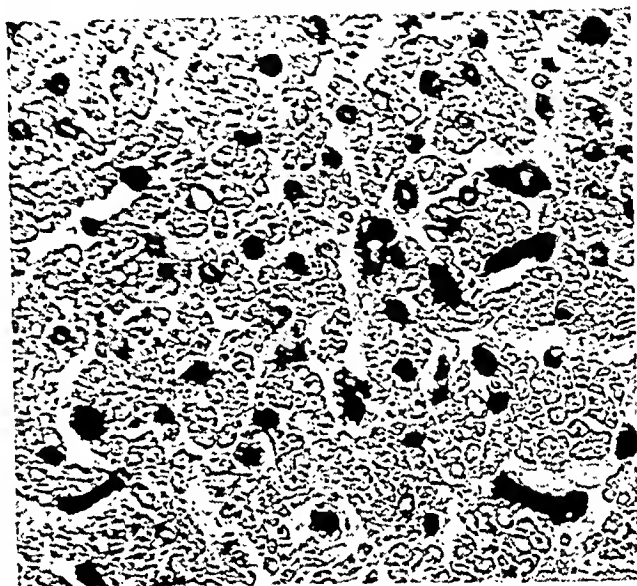


Fig. 1.—Heart weight, 18 Gm. (age 3 weeks). Average fiber diameter, 8.4  $\mu$ . Capillaries, 4,458 per square millimeter. FC ratio, 3.81. (This section was fixed and mounted in such a manner as to show the size of the fibers.)

With these observations in hand, it now becomes possible, by deduction, to point out the changes that occur in the myocardial capillaries during physiologic growth of the heart. If the muscle fibers increase in diameter and not in number, and there is a concomitant decrease in the FC ratio, while the capillary concentration remains constant, it is obvious that the capillaries must multiply in order to maintain the capillary concentration at a constant figure as the muscle mass grows. At birth there is approximately one capillary to each four or five muscle fibers, but when adult life is reached, there is approximately one capillary for each muscle fiber. To summarize, therefore, normal growth of the heart is accompanied by a multiplication of the capillaries at such a rate as to maintain a constant concentration of capillaries in the muscle at all times.

#### NORMAL HEARTS OF ADULTS

In this group of twenty-six patients, death resulted from various diseases, such as pneumonia, meningitis, carcinoma, etc., and some

\*The ratio of the number of muscle fibers per square millimeter to the number of capillaries per square millimeter will be referred to hereafter in this paper as the FC ratio.

died following surgical operations. The ages of the patients ranged from 25 to 77 years, the average age being 49.8 ( $\pm 1.71$ ) years. In the

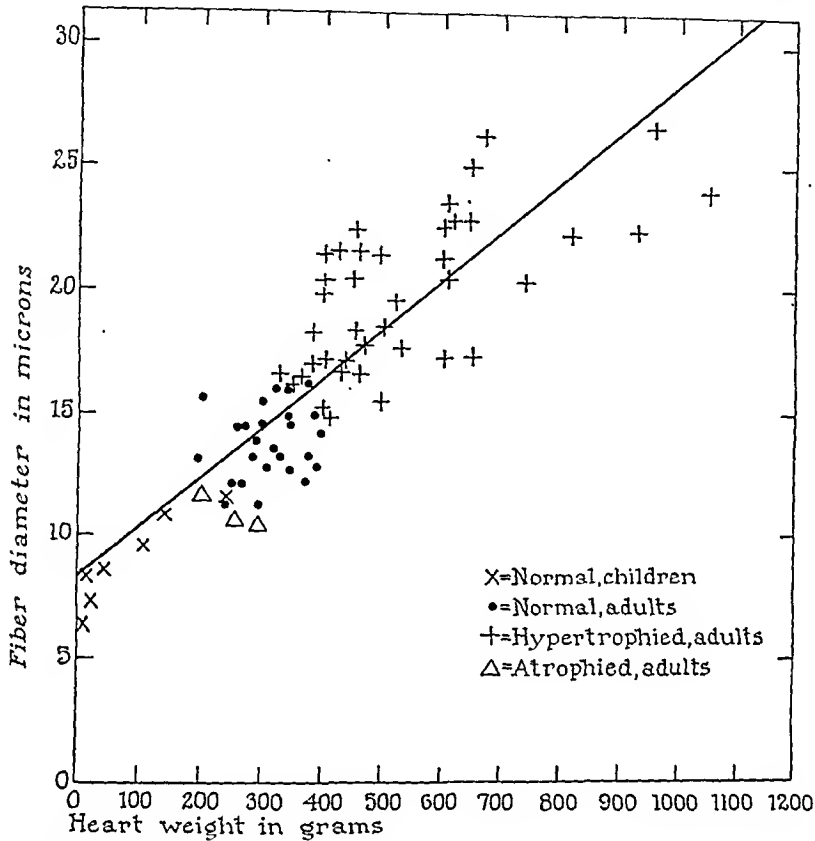


Chart 2.—Relationship of fiber diameter to heart weight during normal growth and hypertrophy of the heart.

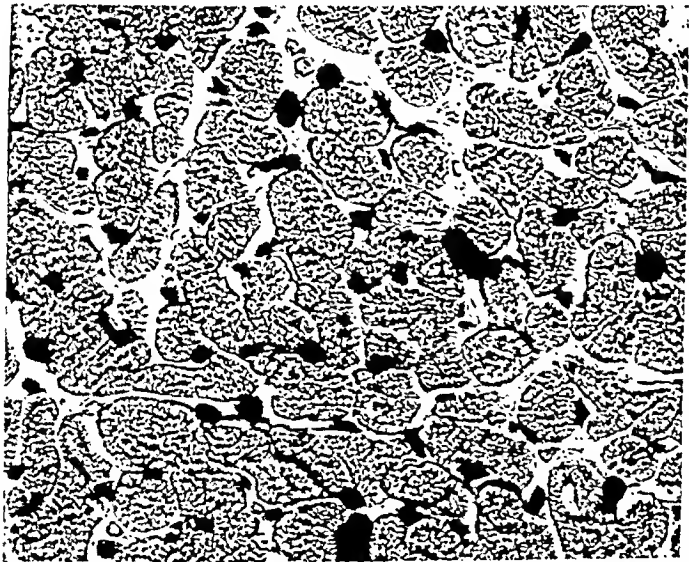


Fig. 2.—Heart weight, 300 Gm. (age 36 years). Average fiber diameter, 15.5  $\mu$ . Capillaries, 3,537 per square millimeter. FC ratio, 1.33.

hearts of several of the oldest patients, arteriosclerotic changes were encountered, but so far as could be determined, this finding did not affect the heart weight, fiber measurements, or capillary counts. The

heart weights ranged from 180 to 400 Gm., with an average of 311 ( $\pm 7.42$ ) Gm. The fiber diameters ranged from 11.5 to 16.1  $\mu$ , with a mean for all hearts in this group of 13.9 ( $\pm 0.2$ )  $\mu$ . In Chart 2, which shows the correlation of the heart weights and the fiber diameters, it will be seen that these normal hearts of adults fall into a compact group.

The number of capillaries per square millimeter in this group of hearts ranged from 2,993 to 4,066, the mean being 3,342 ( $\pm 40$ ). The standard deviation for the entire group is only 8.1 per cent of the mean, which would indicate a fairly uniform concentration of capillaries throughout the group (Fig. 2). When one considers the range in the ages of these patients and the variety of diseases from which they died, and the fact that varying degrees of imperceptible terminal agonal dilatation of the hearts may have occurred, the narrow limits of dispersion of the capillary counts about the mean are of significance.

TABLE II  
NORMAL ADULT HEARTS

NO.	HEART WEIGHT (GM.)	AGE (YR.)	HEART WEIGHT- BODY WEIGHT RATIO	FIBER DIAMETER ( $\mu$ )	CAPILLARIES PER SQ. MM.	FIBER- CAPILLARY RATIO
H29L	180	39	0.00498	13.4	3,114	1.68
39	200	75	0.00740	15.7	3,231	1.29
87	248	59	0.00620	12.2	3,308	1.36
69	262	42	0.00605	14.5	3,405	1.20
83	264	44	0.00427	11.8	3,194	1.26
79	268	52	0.00403	14.4	3,590	1.18
89	275	77	0.00618	12.1	3,414	1.28
45	280	34	0.00400	14.0	4,066	1.36
74	280	58	0.00508	13.2	3,260	1.51
19	290	34	0.00420	11.5	3,390	1.25
46	300	55	0.00380	14.5	3,582	1.46
30	300	36	0.00770	15.5	3,551	1.33
91	304	40	0.00502	13.0	3,030	1.32
58	320	61	0.00689	13.9	3,707	1.05
57	324	25	0.00497	16.0	3,267	0.97
41	326	49		13.6	3,409	1.55
21	336	71	0.00658	14.9	3,092	1.10
47	340	40	0.00790	14.8	3,179	1.46
48	340	40	0.00790	15.9	3,179	1.32
25	342	58	0.00497	13.0	3,368	1.20
72	372	59	0.00490	12.2	3,486	1.36
51	375	59	0.00221	16.1	3,089	1.60
17	375	39	0.00481	13.4	2,995	1.38
84	384	48	0.00548	13.0	2,993	1.36
53	390	58	0.00535	14.3	3,066	1.66
33	400	42	0.00497	15.2	3,939	1.41
Average	310.5	49.8	0.00543	13.9	3,342.5	1.34

There was likewise a remarkable uniformity in this group in the ratio of the number of muscle fibers per square millimeter to the number of capillaries per square millimeter. This FC ratio ranged from

0.97 to 1.68, with an average of 1.34 ( $\pm 0.03$ ) muscle fibers supplied by each capillary. The remarkable uniformity of this figure throughout this group of normal hearts of adults is in striking contrast to the constantly changing figure found for the hearts of growing children. It seems clear, therefore, that once the growth of the heart is completed, the numerical relationship of the fibers and capillaries becomes and remains constant, so long as the heart muscle remains normal.

Several of the adult hearts might well have been placed in either the normal or hypertrophied group. Their classification was decided upon after careful study of the history, autopsy findings, heart weight-body weight ratio, and fiber diameter in each instance. The weights of these hearts were in the region of 400 Gm., and they account for the overlapping of the fiber diameters and the capillary counts in the normal and hypertrophied groups. Exchanging the grouping of any of these doubtfully classified hearts, however, would not affect significantly any of the statistical conclusions derived.

The inclusion of one heart (No. 30) in the group of normal hearts also calls for an explanation. The valves were the seat of mild chronic rheumatic valvulitis and subacute bacterial endocarditis, but there was no hypertrophy, and the heart weight-body weight ratio, muscle fiber measurements, and capillary counts fell within the normal range.

#### HYPERTROPHIED HEARTS OF ADULTS

In the group of patients with hypertrophied hearts there was, in every instance, both clinical and pathologic evidence of heart disease. Hypertension, rheumatic fever, syphilis, and arteriosclerosis of the coronary vessels were the most common causes of the cardiac hypertrophy. In the majority of these patients death resulted from congestive heart failure. In a few of the hearts the weights were such that they might well have been placed in the borderline group described above, but the presence of heart disease and of definite, though slight, hypertrophy seems sufficient reason for placing them in this class.

The age distribution in this group was almost identical with that of the normal adult group, the range being from 18 to 77 years, with a mean of 51.0 ( $\pm 1.55$ ) years. The mean for the normal adult group was 49.8 years.

The weight of the hearts ranged from 326 to 1,050, with a mean of 538 ( $\pm 18$ ) Gm. The average muscle fiber diameters ranged from 14.8 to 26.5  $\mu$ , with a mean of 19.9 ( $\pm 0.30$ )  $\mu$ . As will be seen in Chart 2, there is a direct proportion between the heart weight and the muscle fiber diameter in these hypertrophied hearts. It is obvious, of course, that both of these figures fall well above the ranges for the heart weights and muscle fiber diameters in the group of normal hearts.

The finding of greatest interest and importance was the definite decrease in the concentration of capillaries in the hypertrophied hearts.

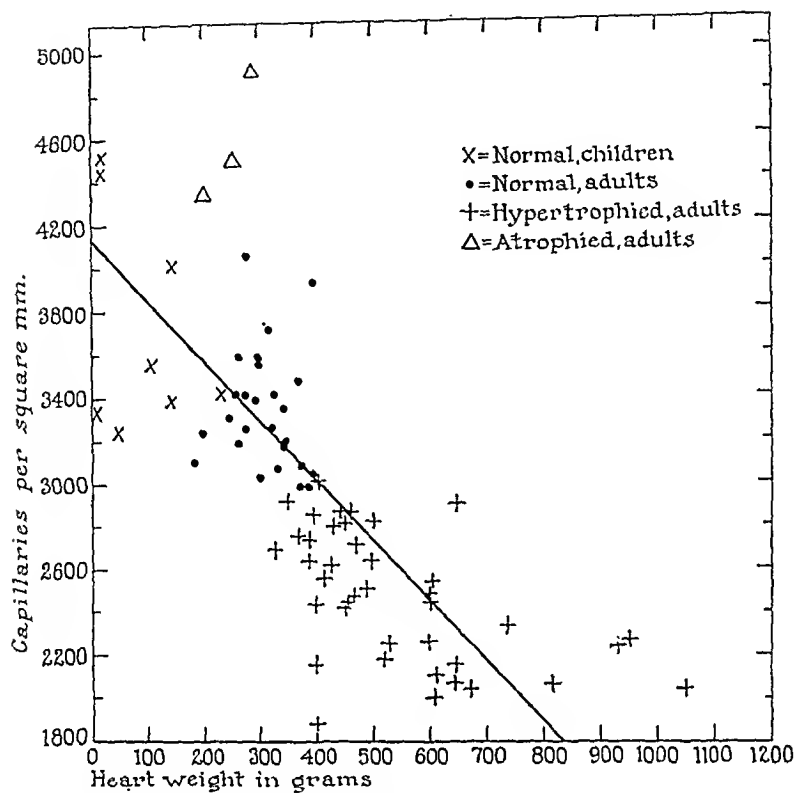


Chart 3.—Concentration of capillaries in normal, hypertrophied, and atrophied hearts.

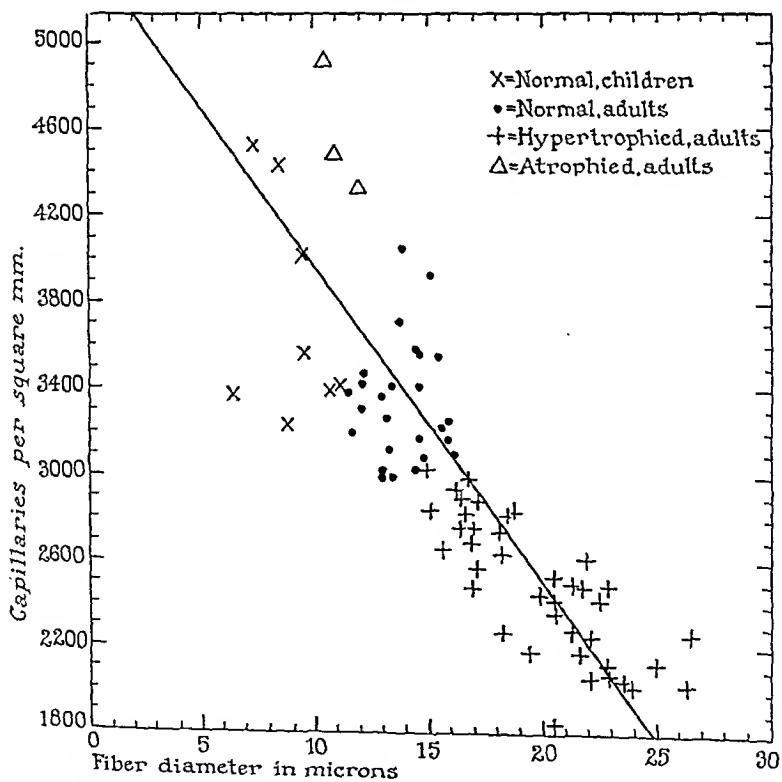


Chart 4.—Relationship of the concentration of capillaries to fiber diameter in normal, hypertrophied, and atrophied hearts.

The capillary concentration ranged from 1,868 to 3,037 per square millimeter, with a mean of 2,483 ( $\pm 31$ ). A comparison of these figures with those of the normal hearts of adults and children (Charts 3 and 4) shows that the trend of the figures for the capillary concentration of hypertrophied hearts is conspicuously lower than those of the normal hearts. The decrease in capillary concentration was clearly due to the increase in diameter of the muscle fibers which, as they enlarged, pushed the capillaries farther apart (Figs. 3 and 4). Moreover, the concentration of capillaries diminished in proportion to the increase in fiber diameter and heart weight.

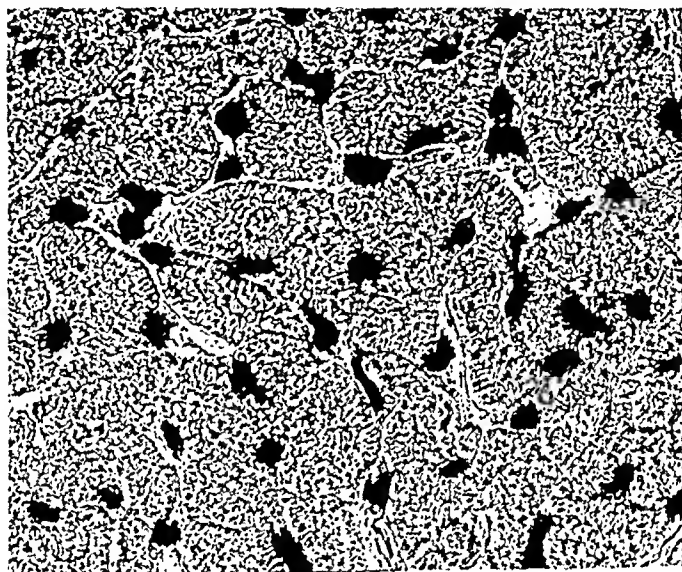


Fig. 3.—Heart weight, 600 Gm. (age 63 years). Average fiber diameter, 22.8  $\mu$ . Capillaries, 2,485 per square millimeter. FC ratio, 1.13.

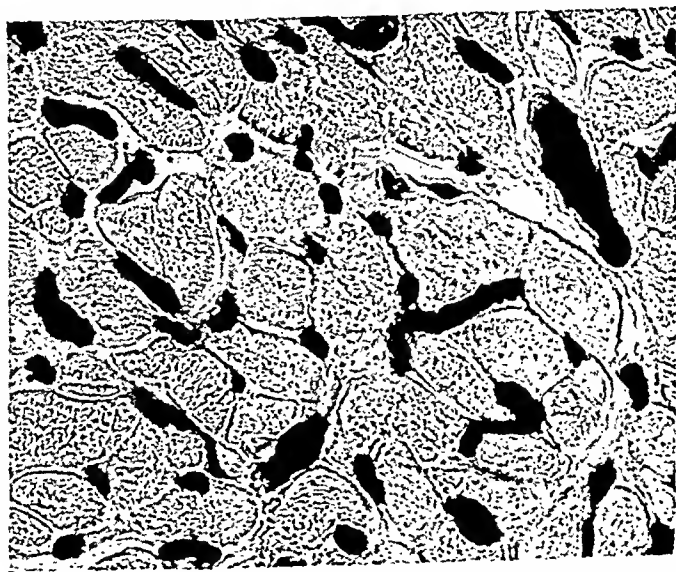


Fig. 4.—Heart weight, 960 Gm. (age 33 years). Average fiber diameter, 26.5  $\mu$ . Capillaries, 2,270 per square millimeter. FC ratio, 1.08.

The remarkable uniformity of the fiber-capillary ratio observed in the normal hearts of adults also held true in the hypertrophied hearts.

TABLE III  
HYPERTROPHIED ADULT HEARTS

NO.	HEART WEIGHT (GM.)	AGE (YR.)	HEART WEIGHT- BODY WEIGHT RATIO	FIBER DIAMETER ( $\mu$ )	CAPILLARIES PER SQ. MM.	FIBER- CAPILLARY RATIO
H70L	326	43	0.00465	16.7	2,694	1.50
43	350	53	0.00745	16.1	2,922	1.65
80	370	64	0.00587	16.3	2,748	1.13
56	380	44	0.00595	18.2	2,640	1.44
61	380	18	0.00792	17.0	2,745	1.38
44	390	52	0.00557	15.1	2,847	1.58
15	400	51	0.00743	19.8	2,438	1.05
16	400	39		21.7	2,173	0.97
13	400	41	0.00687	20.5	1,868	1.57
32	409	66	0.00902	14.8	3,037	1.57
81	415	68	0.00486	17.2	2,558	1.16
14	425	59	0.00810	21.9	2,612	1.12
68	430	46	0.00796	16.7	2,821	1.26
92	439	77	0.00655	17.2	2,874	1.42
65	450	64	0.00958	18.5	2,819	1.16
18	450	44	0.00500	20.5	2,413	1.10
66	455	41	0.00723	22.5	2,430	1.08
71	460	54	0.00523	16.4	2,892	1.49
60	464	67	0.00930	21.8	2,470	1.04
54	470	28	0.00795	18.0	2,727	1.21
42	487	62	0.00715	21.4	2,494	1.26
94	493	24	0.00778	15.7	2,647	1.37
28	500	59	0.00910	18.7	2,835	1.29
78	521	50	0.01023	19.4	2,186	1.18
90	529	29	0.00762	18.1	2,260	1.35
26	600	71	0.00925	17.2	2,488	1.36
27	600	49	0.00822	21.2	2,264	1.28
40	600	63	0.00790	22.8	2,477	1.13
67	604	56	0.01109	20.6	2,526	1.05
86	608	41	0.01030	23.6	2,063	1.02
82	614	66	0.00627	22.9	2,115	0.99
63	645	45	0.00965	22.9	2,082	1.20
75	647	52	0.00880	25.0	2,139	1.05
37	650	76	0.01140	16.9	2,959	1.22
59	670	62	0.01265	26.3	2,040	1.02
93	735	43	0.01234	20.3	2,352	1.22
55	820	70	0.01200	22.1	2,077	1.30
52	930	43	0.01691	22.1	2,257	1.36
38	960	33	0.01433	26.5	2,270	1.08
97	1050	27	0.01690	23.8	2,073	0.89
Average	538.2	51	0.00878	19.86	2,483.4	1.24

The average number of fibers supplied by each capillary was 1.24 ( $\pm 0.020$ ), with a range of 0.89 to 1.65. Thus, the average FC ratio of hypertrophied hearts is remarkably close to that of the normal hearts of adults (1.34). Whether this slight difference is of any significance statistically, we are not prepared to say. From a practical viewpoint, however, the evidence seems convincing that the capillaries do not multiply during hypertrophy to keep pace with the increase in the muscle mass, as they do during normal growth of the heart. With the decrease in capillary concentration in an hypertrophied heart,



each capillary is called upon to supply a larger mass of muscle, and this mass increases proportionately with the weight of the heart.

#### ATROPHIED HEARTS OF ADULTS

There were three hearts which showed atrophy of the muscle. Death in these instances resulted from carcinoma, cerebral hemorrhage, and peritonitis, and at the time of death, marked generalized emaciation was noted. In two of the hearts a moderate amount of arteriosclerosis was present, but otherwise no abnormalities were found. The capillary concentration, fiber size, etc., are shown in Table IV.

TABLE IV  
ATROPHIED ADULT HEARTS

CASE	HEART WEIGHT (GM.)	AGE (YR.)	HEART WEIGHT-BODY WEIGHT RATIO	AVERAGE FIBER DIAMETER	CAPILLARIES PER SQ. MM.	FIBER-CAPILLARY RATIO
H31L	200	71	0.00294	11.9	4,379	1.48
35	257	70	0.00505	10.9	4,515	1.76
36	285	49	0.00500	10.5	4,946	1.83
Average	247.3	63.3	0.00433	11.1	4,613.3	1.69

TABLE V  
CHANGES IN THE CAPILLARIES AND FIBERS

	HEARTS OF CHILDREN	HEARTS OF ADULTS		
		NORMAL	HYPERTROPHIED	ATROPHIED
Number of cases	8	26	40	3
Heart weight (Gm.)	90.8 ( $\pm 19.0$ )	310.5 ( $\pm 7.42$ )	538 ( $\pm 18$ )	247.3
Age (years)	5.91 ( $\pm 1.52$ )	49.8 ( $\pm 1.7$ )	51.0 ( $\pm 1.55$ )	63.3
Fiber diameter ( $\mu$ )	8.96 ( $\pm 0.38$ )	13.9 ( $\pm 0.2$ )	19.86 ( $\pm 0.30$ )	11.1
Capillaries/sq. mm.	3744 ( $\pm 122$ )	3342 ( $\pm 40$ )	2483 ( $\pm 31$ )	4613
Fibers per capillary	3.23 ( $\pm 0.32$ )	1.34 ( $\pm 0.03$ )	1.24 ( $\pm 0.02$ )	1.69

This group is too small to justify any conclusions, but in all three cases where there was cardiac atrophy, the average size of the muscle fibers was smaller than normal and the concentration of capillaries was increased above the normal figure. The obvious interpretation is that, with the decrease in size of the muscle fibers, the capillaries lie closer together. In these three instances the FC ratios were abnormally high, but our observations do not furnish any explanation for these findings.

#### DISCUSSION

When one studies the data presented in this report bearing upon the quantitative relationship of the capillaries to the heart muscle mass, it becomes obvious that a high order of correlation exists; so high, indeed, that it strongly suggests an underlying biologic law

which may govern these processes. Between the average fiber diameter and the number of capillaries per square millimeter, for instance, there is a very close correlation. This takes the form of a high negative rectilinear correlation, the coefficient of which is "minus 0.839 ( $\pm 0.023$ ).'' From the regression lines, the capillary concentration in the heart can be calculated from the known average fiber diameter by the following formula:

Capillaries per square millimeter =  $3947 - (119.95 \times \text{fiber diameter})$   
 The probable error for the predicted value is  $\pm 225$  capillaries per square millimeter. For the most part, the figures for our individual hearts, as shown in Chart 4, show very little deviation from the plotted straight line of closest fit.

There is also a high positive (i.e., direct) rectilinear correlation between the heart weight and the average muscle fiber diameter. The correlation coefficient, with its probable error, for these two is "plus 0.872 ( $\pm 0.019$ ).'' If the heart weight is known, the average muscle fiber diameter can be calculated by the formula:

$$\text{Fiber diameter} = 8.22 + (0.0199 \times \text{heart weight})$$

The probable error for the predicted value is only  $\pm 1.51 \mu$ . This correlation is rectilinear, and, as will be seen in Chart 2, all of our individual observations fall very close to the plotted straight line of closest fit.

Since these two correlations exist, a very close correlation between the actual heart weight and the capillary concentration would naturally be expected. This proved to be a high degree of negative rectilinear correlation, with a correlation coefficient and its probable error of "minus 0.745 ( $\pm 0.035$ ).'' The capillary concentration per unit of area can be calculated from the actual heart weight by the formula:

$$\text{Capillaries per square millimeter} = 3,975 - (2.425 \times \text{heart weight})$$

The probable error for the predicted value is  $\pm 295$  capillaries per square millimeter. For the most part our cases show little dispersion from the plotted straight line of closest fit. The explanation of the dispersion of the few that deviate more widely is clear when the fiber size and the clinical and pathologic conditions are considered.

From our data, the correlation between the age of the subject and the FC ratio also appears to be a close one. In this instance the correlation is a negative one and is curvilinear, the curved line of closest fit for our data resembling an hyperbolic type of curve similar to those frequently encountered in studies of growth phenomena (see Chart 1). The correlation ratio, with its probable error for age (X) and the FC ratio (Y), is expressed by the formula:

$$Eta_{YX} = 0.914 (\pm 0.015)$$

The FC ratio may be predicted from the patient's known age by the formula:

$$\text{FC ratio} = \frac{5.67}{\text{Age} - 0.14} + 1.20$$

The portion of the curve on the right side of Chart 1, i.e., the part dealing with the adult hearts, is practically a horizontal straight line. The curve indicates very clearly the two types of vascular change during enlargement of the heart. The first is the multiplication of capillaries, which maintains a constant capillary concentration during the physiologic growth period of the heart, and the second is the actual decrease in the capillary concentration which occurs when the heart hypertrophies as a result of disease. These results, although based upon results in a small number of children's hearts, are in agreement with those of Shipley, Shipley and Wearn.<sup>19</sup>

The amount of connective tissue lying between the muscle fibers and the capillaries in the large muscle planes did not vary significantly in the normal and hypertrophied hearts. This tissue was estimated by means of the ocular micrometer. The average percentage of interstitial connective tissue in the hearts of the children was 3.15; in the normal hearts of adults, 4.54; and in the hypertrophied hearts, 4.61. It should be pointed out that the method of measurement did not include observations on the large connective tissue septal sheaths lying between the muscle planes.

Our method of counting capillaries and measuring muscle fibers called for an even distribution of muscle fibers and a complete injection of the capillary bed. These requirements eliminated those areas in the sections which contained large fibrous and necrotic scars resulting from arteriosclerosis or rheumatic fever. We have purposely confined this report to the observations on the unscarred normal and hypertrophied muscle. (The effect of arteriosclerosis, hypertension, syphilis, and rheumatic fever upon the capillary-fiber relationship, etc., will be reported upon in a separate communication.)

A comparison of the areas of the average muscle fibers is of interest in that it emphasizes the differences between the normal and hypertrophied hearts of the adult group. The average fiber area, based on the formula for the area of an ellipse, was calculated from the measurements of the diameters of the cross section of the individual muscle fibers. The average area of a fiber for the hearts of children of various ages was 63.3 sq.  $\mu$ ; for the hearts of normal adults, 148.4 sq.  $\mu$ ; and for the hypertrophied hearts, 306.5 sq.  $\mu$ .

The average area of tissue supplied by each capillary was found to be 267 sq.  $\mu$  for the hearts of children; 299 sq.  $\mu$  for the normal hearts of adults; and 403 sq.  $\mu$  for the hypertrophied hearts. Thus, the area supplied by each capillary was essentially the same in the hearts of

children and normal adults, but considerably greater in the hypertrophied hearts.

The capillary surface area may be obtained approximately by the formula for the surface of a cylinder 1 cm. in length with a diameter equal to that of the capillary; this, multiplied by the number of capillaries per square centimeter, gives the surface area of the capillaries in 1 c.c. of heart tissue. The diameter of the capillary was assumed in this calculation to be that of a red blood corpuscle in each group of hearts. By this method the capillary surface area per cubic centimeter of tissue was found to be 882 sq. cm. for the children's hearts, 787 sq. cm. for the normal hearts of adults, and 585 sq. cm. for the hypertrophied hearts.

When the muscle fiber volume in 1 c.c. of heart tissue was calculated from the average area of individual fibers and the number of fibers per square centimeter of heart tissue, using the formula for the volume of a cylinder, the percentage of muscle fiber in 1 c.c. of heart tissue was 77 per cent for the children's hearts, 67 per cent for normal hearts of adults, and 94 per cent for hypertrophied hearts.

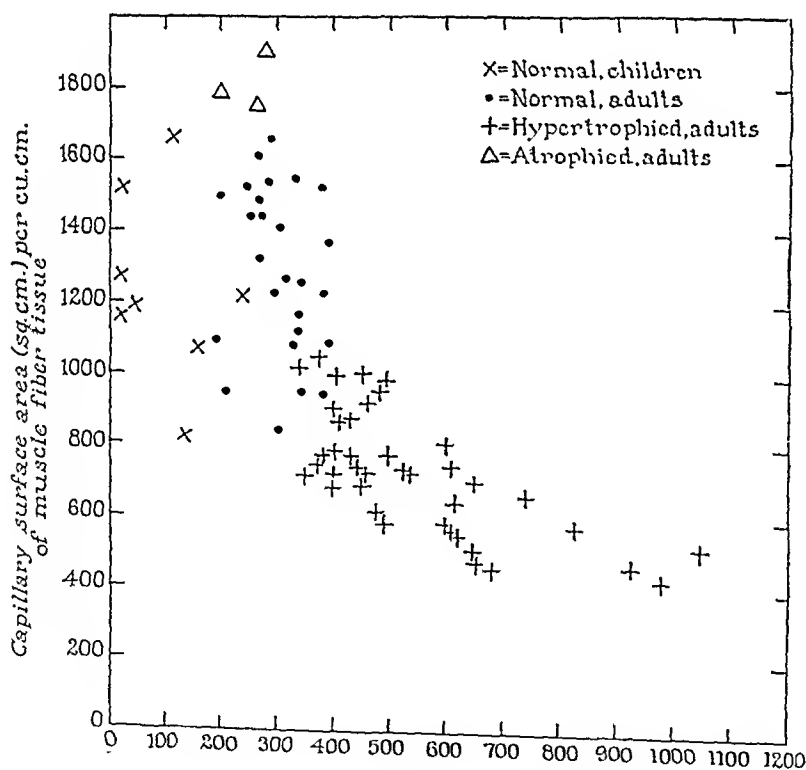


Chart 5.—Capillary surface area in normal, hypertrophied, and atrophied hearts.

The ratio of the capillary surface area to the percentage of muscle tissue per cubic centimeter of heart tissue gives an approximation of the capillary surface area available for diffusion of oxygen and metabolites to and from 1 c.c. of contractile muscle fiber substance. This was

# THE "ANOXEMIA TEST" IN THE DIAGNOSIS OF CORONARY INSUFFICIENCY

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IN A previous communication,<sup>1</sup> it was proposed that changes in the form of the electrocardiogram caused by induced generalized anoxemia might be used as an index of the functional efficiency of the coronary circulation. A simple apparatus suitable for producing oxygen want had already been described.<sup>2</sup> Tentative criteria for an abnormal response were established. Other uses to which the method might be put were suggested. It has already been applied to the study of the effect of various drugs on the coronary arteries in patients with anginal pain and has served to demonstrate the value of certain of these as coronary dilators.<sup>3, 4</sup> In the present paper, further experiences with the "anoxemia test" are related; the criteria for an abnormal response are modified; reactions to induced oxygen want are described; and the limitations, as well as the clinical applications of the test, are discussed.

## TECHNIQUE

For convenience, the apparatus and procedure are again described. The only difference in the apparatus as it is now used is the addition of a humidifier. This has eliminated the dryness of the throat of which a number of patients previously complained. The manner of carrying out the test is unchanged.

*Apparatus* (Figs. 1 and 2).<sup>\*</sup>—A tank containing a mixture of 10 per cent oxygen and 90 per cent nitrogen furnished an unvarying concentration of oxygen in the inspired air.<sup>†</sup> The oxygen mixture was admitted at a rate comparable to that of normal pulmonary ventilation. The gas was allowed to flow, through a humidifier, into a rubber bag, which was kept full, but not distended. Two flutter valves were incorporated in such a way that the mixture was inhaled during inspiration and exhaled during expiration, without rebreathing. A two-way valve at the mouthpiece enabled the observer to connect the patient to the apparatus while he was breathing room air, and thus accurately to record the time at which the subject began breathing the low-oxygen mixture. A tank containing 100 per cent oxygen was also in the circuit, so that, if desired, by turning a needle valve, anoxemia could be relieved quickly.

*Procedure*.—Observations were made at least two hours after the last meal. The temperature of the room in which the test was made was kept reasonably constant

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<sup>\*</sup>The apparatus may be obtained from the Foregger Co., 55 W. 42nd St., New York City.

<sup>†</sup>The tanks of 10 per cent oxygen were obtained from the Ohio Chemical Co. The composition of the mixture was checked at frequent intervals, and was found to vary not more than  $\pm 0.6$  per cent.

at about 72° F.\* The subject was allowed to rest quietly in bed for a period varying from thirty minutes to an hour. The procedure was explained, and he was told that if he experienced pain in the chest or arms he should at once raise his hand. The

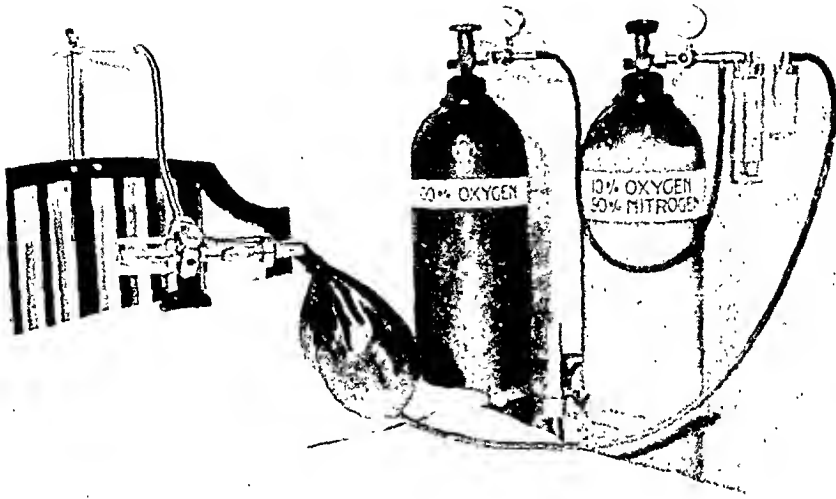


Fig. 1.—Apparatus ready for use.

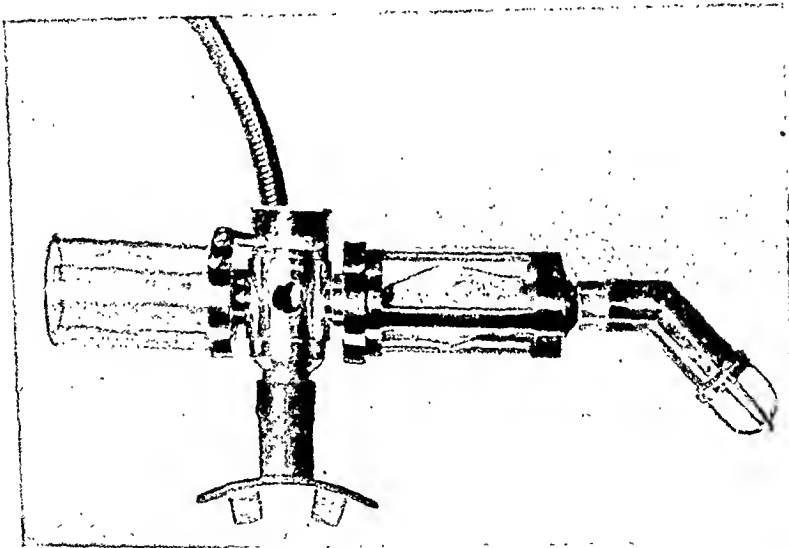


Fig. 2.—Mouthpiece, control valve, flutter valves, and connection for bag.

electrodes were applied and remained in place throughout the test. The mouthpiece of the gas apparatus was then inserted, and a nose clamp adjusted. The subject was

\*In patients who are subject to anginal attacks, exercise tolerance is reduced shortly after taking food, but is unaffected by variations in the external temperature (Wayne, E. J., and Graybiel, A.: Observations on the Effect of Food, Gastric Distension, External Temperature, and Repeated Exercise on Angina of Effort, with a Note on Angina Sine Dolore, Clin. Science 1: 287, 1933-1934). Using our method for inducing anoxemia, it has been shown recently that anginal pain appears earlier when the test is done on a patient with a full stomach than during the fasting state (Gilbert, N. C., Fenn, G. K., and Le Roy, G. V.: The Effect of Distention of Abdominal Viscera on the Coronary Blood Flow and on Angina Pectoris, J. A. M. A. 115: 1962, 1940).

allowed to breathe room air through the valve of the apparatus for a few minutes. At this time a four-lead electrocardiogram was taken as a control. The precordial lead was the one commonly designated as IVF. The test was then started by closing the valve; the subject was unaware of this maneuver. The standard period of inhalation of the 10 per cent oxygen mixture was 20 minutes, for it was found that within this time electrocardiographic changes usually appeared in cases of coronary sclerosis; when the anoxemia was continued longer, the subjects tended to become restless and uncomfortable. Additional electrocardiograms were taken at the end of 5, 10, 15, and 20 minutes. If pain was experienced, or if there were signs of an undesirable reaction at any time during the test, an electrocardiogram was taken at once, the low-oxygen mixture was shut off, and 100 per cent oxygen was administered for approximately one minute. Electrocardiograms were again taken 1, 5, and 10 minutes after the latter procedure, with the mouthpiece still in place and with the patient breathing room air through the control valve.

For ordinary clinical purposes it suffices to take only three records, namely, a control; a second at the end of twenty minutes (or upon the appearance of pain or other discomfort); and a third, five minutes after 100 per cent oxygen has been given for one minute. The last record serves to demonstrate that such changes as may have taken place can be partly or wholly abolished when anoxemia is relieved.

In each lead measurements were made of the deviation of the RS-T junction and the amplitude of the T wave. The direction of the T wave was also indicated. The heart rate was counted in Lead II. Measurement of the P-R and QRS intervals was omitted because it had been previously shown that these did not vary significantly.<sup>1</sup> The data from each test were charted on individual sheets.

Deviation of the RS-T junction, measured in millimeters, was taken as the difference in level between the point just preceding the initial deflection of QRS and the point immediately following its final deflection. In measuring a given record, either the upper or the lower margin of the string shadow was used in establishing both points. Care was taken to select complexes which ran horizontally. All of the records were read independently by at least two observers. A Cambridge string-galvanometer electrocardiograph was employed. Standardization of the string's deflection was accurate, and skin resistances were kept low to avoid overshooting.

#### LITERATURE

In an earlier paper,<sup>1</sup> the work of previous observers was briefly reviewed. It was pointed out that pain induced either by exercise or by oxygen want is an unreliable index of coronary insufficiency, partly because it represents a subjective end point, and also because so many complex factors are concerned in its production. Besides, many patients with disease of the coronary arteries do not experience pain. An objective index of effect is desirable. For this purpose, changes in the electrocardiogram following standard exercise tests have been employed by numerous workers, with positive results in cases of coronary insufficiency. It is difficult to secure reliable electrocardiograms during or immediately after exercise, particularly if four leads are taken; and encouraging patients to exert themselves to the point of discomfort is not entirely without hazard. Tests carried out with the rebreathing method do, indeed, produce alterations in the form of the electrocardiogram,<sup>5, 6, 7</sup> but the percentage of oxygen which is finally reached in the mixture is not fixed, so that accurate comparisons of the effect on the same person at different times, or on different persons, cannot be made.

The observations which are most nearly comparable to those here reported were made by Larsen,<sup>8</sup> who discussed them in an excellent monograph, published in Danish, in 1938. An eleven-page summary is given in English. He permitted patients to breathe a 9 per cent oxygen mixture, prepared by mixing a known amount of atmospheric air with a known amount of nitrogen. The mixture was inhaled for from three to eight minutes. In normal persons the changes in the electrocardiogram were very similar to those here reported. Larsen regarded as abnormal the appearance of diphasic or negative T waves in Lead I, and depression of the S-T segments more than 1 mm. below the isoelectric line in any lead. No precordial lead was employed. In thirteen of seventeen cases in which the diagnosis was "coronary angina pectoris," significant electrocardiographic changes were induced by oxygen want. In nine of these, abnormalities in the tracings were found prior to the test. The changes described were depression of the S-T segments in Lead I or Lead II, or both. The T waves in Leads I and II became diphasic in seven, and of lower amplitude, although still positive, in two. Changes also occurred in the T wave in Lead III. In the other portions of the records, no alterations were found with any degree of regularity. As a rule, the changes disappeared within five or six minutes after the test was terminated.

In four cases the control electrocardiogram showed only slight deviation from the normal, and no modification was produced by anoxemia; but depression of the S-T segments and changes in the T waves appeared after exercise.

There was no constant relationship between the occurrence of pain and electrocardiographic alterations; some patients showed a positive test without pain; others felt pain and showed no graphic changes.

Larsen points out that the absence of an abnormal response during anoxemia does not necessarily imply that the coronary arteries are free from "stenotic lesions." He speculates as to the reasons for this and suggests that perhaps under such circumstances there are lesser degrees of coronary narrowing than are present in those patients who show an abnormal response.

Ten patients over 40 years of age who complained of attacks of pain in the chest and had no objective signs of cardiac disease showed no abnormal changes in the electrocardiogram during anoxemia, but two stated that they felt their customary pain in the chest while the test was being made. It is Larsen's belief that, technically, the anoxemia test offers certain advantages over the exercise test; on the other hand, the exercise test gives a positive result a little more often. He expresses the opinion that every patient who applies for disability claims or social aid because of attacks of pain in the chest is entitled, in case of doubt, to be examined in one or both of the ways just mentioned.

In anemia, he found, as did we,<sup>1</sup> changes similar to those observed in coronary insufficiency caused by coronary sclerosis. He has done the



test in a number of other conditions which are not relevant to this discussion. He concludes that the method is suitable for clinical use and should be carried out under the direction of a physician; and that, when conducted properly, there is no risk to the patient.

The recent experiments of Leslie, Scott, and Mulinos<sup>9, 10</sup> on cats lend support to our observations on patients. After ligation of a coronary branch, characteristic deviation of the RS-T segments invariably appeared in the electrocardiogram. In one group, these changes disappeared in twelve to thirty-two days, but could be reproduced temporarily by having the animals breathe a 10 per cent oxygen mixture. In another group, persistent RS-T deviation after arterial ligation was accentuated by the induction of anoxemia.

#### MATERIAL

In order to establish criteria for the changes in the electrocardiogram which are induced by anoxemia in normal subjects, 115 persons without symptoms or signs of cardiac disease were tested 122 times. In the course of these tests, 976 electrocardiograms were made. The ages of these normal subjects ranged from 21 to 78 years.

TABLE I  
MATERIAL STUDIED

	NUMBER OF CASES	NUMBER OF EKGS TAKEN	NUMBER OF TESTS
Normals	115	976	122
Patients	147	1340	204
Totals	262	2316	326

TABLE II  
AGE AND SEX DISTRIBUTION

AGE GROUPS	NORMALS		PATIENTS	
	MALE	FEMALE	MALE	FEMALE
21-30	47	6	1	0
31-40	12	2	8	5
41-50	17	2	32	17
51-60	13	8	33	13
61-70	4	1	27	8
71-80	1	2	1	1
Totals	94	21	102	44

(Age of one man not recorded.)

In 147 cases of suspected or manifest cardiac disease caused by coronary sclerosis or hypertension, 204 tests were done, in the course of which 1,340 electrocardiograms were taken. The age range was the same as in the normal group, although the distribution in the various decades was not identical. Obviously, it was easier to find normal subjects in the younger age groups; and patients with coronary sclerosis were more numerous after the age of 40 years. There was the usual predominance of males among the cardiae, and this relative preponderance was maintained in the normals (Tables I and II).

The patients were classified entirely on the basis of clinical observation before the anoxemia test was carried out. The form of the electrocardiogram and the size

of the heart, as measured in the teleroentgenogram, were included in the examination. The patients who were grouped under the caption "coronary sclerosis suspected" comprised those with a history suggestive of anginal pain, but with no signs of cardiac disease and with a normal electrocardiogram. The patients with "coronary sclerosis without pain" showed either an abnormal electrocardiogram or cardiac enlargement, or both. In some of these cases, previous cardiac infarction was known or believed to have occurred. Similar signs were present in the group labelled "coronary sclerosis with pain"; and among these patients, too, there were some with healed infarcts. Of the nineteen patients with "hypertension," nine had normal electrocardiograms, and ten showed changes which were not regarded as indicative of coronary sclerosis. None of the hypertensives were considered, clinically, to be suffering from coronary insufficiency.

#### CRITERIA INDICATING CORONARY INSUFFICIENCY

It was pointed out previously that, in normal persons, during induced anoxemia, the T waves tend to decrease in amplitude.<sup>1</sup> There may also be partial or complete reversal in the direction of T in Lead II or Lead III, or both. It is known that emotion, especially fear, may affect the form of the electrocardiogram. Among others, Rühl<sup>11</sup> and Mainzer and Krause<sup>12</sup> have shown that, under such stress, changes sometimes occur in both T waves and RS-T segments. That this should be so is not surprising, for, according to Cannon,<sup>13</sup> emotions cause a discharge of epinephrine; and this, in turn, increases the rate and work of the heart. Epinephrine also is known to produce alterations in the caliber of the coronary vessels, as well as changes in the form of the electrocardiogram.<sup>14, 15</sup> In a number of our subjects who were regarded as normal, and especially in the younger age groups, changes in the electrocardiogram were observed during the first test which were not present, or were of lesser degree, when the test was repeated. Presumably, the apprehension which was felt because of the novelty of the experience was absent the second time. Variations in the effects of anoxemia on the electrocardiogram may also be caused by differences in the depth and rate of respiration during any one test, or in the same person at different times. As a result, the degree of anoxemia which is induced is probably not always the same. In an earlier study,<sup>2</sup> in tests with a mixture containing 12 per cent oxygen, it was shown that there was no constant relationship between the time of occurrence of anginal pain and the level of arterial oxygen unsaturation. Observations correlating this level with the appearance of electrocardiographic changes have not yet been made.

The criteria for an abnormal response were made sufficiently rigid so that normal subjects who showed such variations were excluded from the group with coronary insufficiency. We have thought it wiser, for the present, to err in allowing for a relatively wide range of normal, rather than mistakenly to label as "positive" certain doubtful, borderline tests. It was perhaps on this account, as will be apparent presently, that the percentage of positive tests among the patients with coronary disease was not higher.

*Criteria of an Abnormal Response.*—Judging from our experience to date, the test should be considered positive when any one of the following is observed:

1. The arithmetic sum of the RS-T deviations in all four leads (I, II, III, and IVF) totals 3 mm. or more.
2. There is partial or complete reversal of the direction of T in Lead I, accompanied by an RS-T deviation of 1 mm., or more, in this lead.
3. There is complete reversal of the direction of T in Lead IVF, regardless of RS-T deviation.
4. There is partial reversal of the direction of T in Lead IVF, accompanied by an RS-T deviation of 1 mm., or more, in this lead.

The change most frequently noted was criterion 1, which occurred as the only sign in thirty-two of eighty-eight positive tests. Next in the order of frequency were combinations of criteria 1, 2, and 4; 1 and 3; and 1 and 4, which occurred 13, 11, and 10 times, respectively. Criterion 3 occurred as an isolated change eight times. All four criteria were never encountered together in the same case. Examples of the various types of change are shown in Figs. 3 and 4.

TABLE III

INCIDENCE OF POSITIVE TESTS AND OF PAIN IN VARIOUS CLINICAL GROUPS

	CONTROL EKG	TOTAL NO. OF CASES	CASES IN WHICH TESTS WERE POSITIVE			PAIN DURING TEST	
			NUMBER	PER CENT	COM- BINED PER CENT	NUMBER	PER CENT
Coronary sclerosis suspected	Normal	33	6	18	18	12	28
Coronary sclerosis without pain	Normal	5	1	20			
	Abnor- mal	17	7	41	31	2	10
Coronary sclerosis with pain	Normal	24	10	42			
	Abnor- mal	49	34	69	55	46	63
Hypertension	Normal	9	0	0			
	Abnor- mal	10	1	10	5	1	5
Totals		147	59			61	

## RESULTS (TABLE III)

*Coronary Sclerosis Suspected.*—Of thirty-three subjects, six, or 18 per cent, gave a positive test. In twelve cases, or 36 per cent, pain occurred during the test. Pain, in this group, was more often induced than were changes in the form of the electrocardiogram.

*Coronary Sclerosis Without Pain.*—This group was divided into two categories. In the first, the control electrocardiogram, which was taken before the test, was normal; in the second, it was abnormal. By abnormal it is meant that significant T-wave negativity, bundle branch

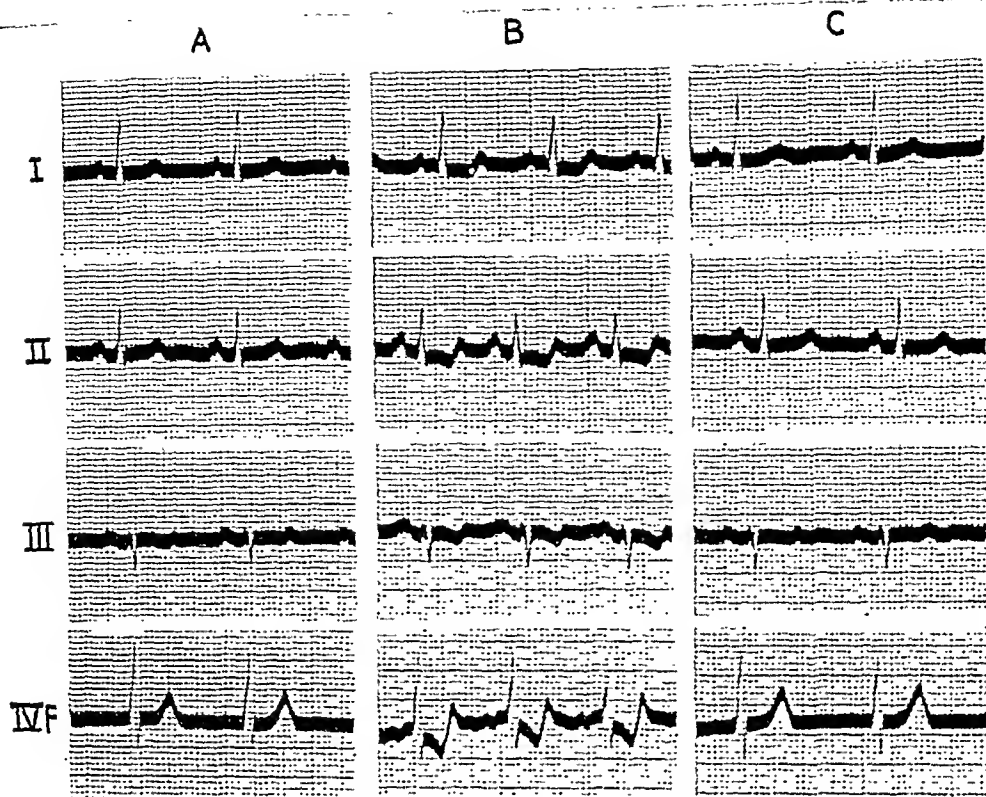


Fig. 3.—Male, aged 48 years, had coronary sclerosis with pain. Test was positive; criteria 1 and 4 present. A, Control. B, After thirteen minutes of anoxemia; pain. C, Five minutes after 100 per cent oxygen had been given for one minute.

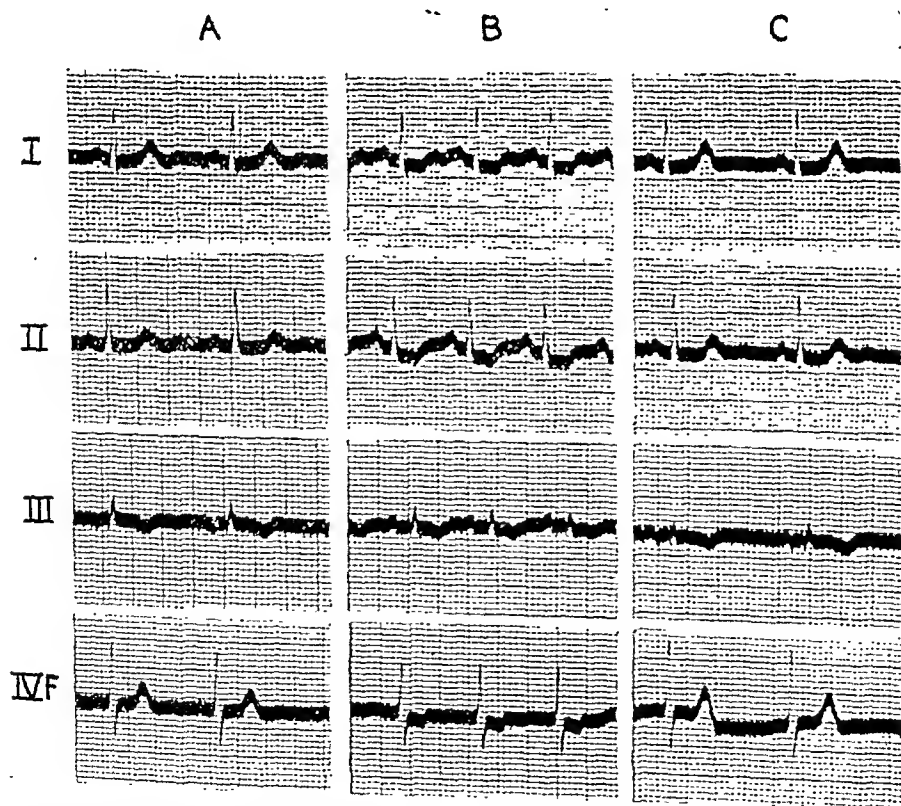


Fig. 4.—Female, aged 54 years, had coronary sclerosis with pain. Test was positive; criteria 1, 2, and 3 present. A, Control. B, After twenty minutes of anoxemia; no pain. C, Five minutes after 100 per cent oxygen had been given for one minute.

block, changes in the level of the RS-T segments, or combinations of these were present. Of five subjects in the first category, only one, or 20 per cent, showed a positive test. Of seventeen in the second category, seven, or 41 per cent, showed a positive test. An abnormal control electrocardiogram probably indicates more extensive impairment of the coronary bed, so that a higher percentage of positive tests might have been anticipated. Of twenty-two subjects in the group as a whole, 31 per cent showed a positive test and only two, or 10 per cent, experienced pain.

*Coronary Sclerosis With Pain.*—Of twenty-four patients with normal control electrocardiograms, ten, or 42 per cent, showed a positive test. Of forty-nine with abnormal control electrocardiograms, thirty-four, or 69 per cent, showed a positive test. Again, those with abnormal control records showed the higher incidence of positive tests. In the group of seventy-three subjects, as a whole, 55 per cent showed positive tests, and 63 per cent experienced pain.

*Hypertension.*—Of nine patients with a normal control electrocardiogram, none showed a positive test. Of ten patients with an abnormal control electrocardiogram, only one showed a positive test; and this same patient experienced pain. It should be recalled that cases of hypertension in which there was clinical evidence of coronary sclerosis were excluded. In one instance it appears that the clinical diagnosis, in this respect, was incorrect.

*All Groups.*—The heart rate rose 10 beats, or more, in almost all cases during anoxemia. In only two cases did the rate fall; in a small number there was no change. In a majority of the cases (64 of 113 tests, or 56 per cent) there was a rise in systolic blood pressure of more than 10 mm. Hg. In a few the pressure fell; in about one-third there was a change of less than 10 mm. Hg. The trend of the heart rate and blood pressure bore no relationship to the outcome of the test or to the occurrence of pain. All combinations of these factors were encountered.

There was no demonstrable relationship between the size of the heart and the occurrence of a positive test.

#### REACTIONS TO THE TEST

All of the patients became moderately cyanotic; the degree of cyanosis varied. In a previous paper,<sup>1</sup> two cases of pulmonary edema which occurred during the test were described. Early in the course of the present study, one additional case was observed. All three recovered promptly following a hypodermic injection of morphine and rest in the overnight ward. Including our work on drugs, part of which has already been published,<sup>3, 4</sup> we have performed the test over 600 times, and have encountered this untoward reaction on only these three occasions. Troublesome effects have been avoided by observing three simple rules:

1. The test should never be performed in the presence of congestive heart failure.

2. It should not be performed within 4 months after cardiac infarction.

3. It should not be done on the same patient more than once in twenty-four hours.

Unpleasant effects have been observed twenty-four times in seventeen cases; of these subjects, five were normal persons and twelve were patients with coronary sclerosis.

A. *Vasovagal reactions*.—These occurred twelve times in eleven cases, and were characterized by subjective sensations usually described as "faintness." This was accompanied by slowing of the pulse rate, fall in blood pressure, coldness of the skin, pallor, and sweating. These manifestations varied in degree from slight discomfort to a state of extreme weakness. Usually, however, the reaction was mild because its onset was recognized, the test was discontinued, and 100 per cent oxygen was promptly given. Minor T-wave variations at the height of the reaction were common. "Positive" changes appeared only twice; in both instances, with the onset of the attack, they disappeared. In one of these cases, A-V nodal rhythm replaced the sinus mechanism during the attack; in the other, A-V conduction time was prolonged temporarily from 0.15 to 0.24 second.

The attacks, in their manifestations, indicated disturbance of both vagus and sympathetic systems. That both of these, as well as the carotid sinus reflex, may be affected by anoxemia has been convincingly shown by Gellhorn and Lambert.<sup>16</sup> The clinical picture is similar to that described by Lewis<sup>17</sup> as "vasovagal syncope," except that fainting did not occur. Its failure to appear may have been caused, in part, by the fact that the patients were recumbent, and, in part, by aborting the attack with pure oxygen. Graybiel, et al.,<sup>18</sup> have described a similar "fainting" type of reaction during the inhalation of a 12 per cent oxygen mixture in a case of hypertensive heart disease and slight secondary anemia. In this case, after breathing the mixture for five minutes, there was a sharp fall in pulse rate and in systolic and diastolic blood pressures; pallor and cyanosis were followed by syncope.

B. *Convulsive seizures*.—These were observed twice. They were mild and lasted less than one minute. In one instance, the seizure was clearly hysterical; it occurred in an emotionally unstable woman, 45 years of age, after she had breathed a 10 per cent oxygen mixture for ten minutes. The RS-T segments were not depressed, but the T waves decreased slightly in amplitude. The attack was characterized by rigidity and tremors of the muscles, without hyperreflexia or hyperventilation. Both the pulse rate and blood pressure rose. The second patient was a 44-year-old negro, who, after five minutes of anoxemia, developed a clonic convulsion and positive electrocardiographic changes. There occurred,

in sequence, pallor of the mucous membranes, tachycardia, and syncope, but there was no significant alteration in blood pressure. Both patients recovered completely within a few minutes.

*C. Hyperventilation.*—This was observed seven times in two cases. There was no associated change in pulse rate or blood pressure. In one case, pain was experienced without electrocardiographic changes. The second patient, who had a healed cardiac infarct, reacted in this fashion on six different occasions; four positive tests were followed by two negatives. The latter were obtained after clinical improvement had taken place.

*D. Dyspnea.*—In two tests on a 59-year-old white man, whose electrocardiogram showed left bundle branch block, pain developed; at the same time, his respirations became deep and labored. Anoxemia had to be discontinued after five minutes on one occasion, and after eleven minutes the second time. Both tests were negative, probably because the duration of anoxemia was too short. There was no change in pulse rate or blood pressure.

*E. Mental confusion.*—This was observed once in the case of a 74-year-old woman with manifest cerebral arteriosclerosis. It lasted less than fifteen minutes. In the previous series of cases<sup>1</sup> this was recorded as a transient occurrence in two cases, in both of which the patient was believed to have sclerotic cerebral vessels.

None of these reactions was serious or harmful. The vasovagal seizures were disturbing until we became familiar with them. If the test was promptly stopped when pallor, sweating, coldness of the skin, or marked slowing of the pulse rate was noted, and 100 per cent oxygen was given promptly, the attack could be aborted. Patients who show any of these types of reaction during the first test should not be subjected to the procedure a second time. We repeated the observations six times in the case of the subject who hyperventilated because he did not object and did not appear to suffer any ill effects.

#### COURSE AND NECROPSY PROTOCOLS OF PATIENTS WHO SUBSEQUENTLY DIED

Of the 147 patients, nine have died. Death occurred from four weeks to twenty-one months after the last test was done. Five of the nine patients died suddenly. On one of these five, the test was done twenty-one months prior to death, but had to be discontinued at the end of seven minutes because of a paroxysm of coughing. No electrocardiographic changes had appeared at this time, although the man was known to have a healed myocardial infarct. The other four patients in this group showed positive tests.

The test was negative on one patient with hypertension. He died at home, of congestive heart failure, five months later. One patient with a positive test died three months afterward, of coronary occlusion.

Necropsy was performed in two cases. Brief abstracts of the clinical and pathologic records follow.

CASE 1.—F. B., Unit No. 402171. A white man, aged 67, complained of dyspnea on exertion and precordial oppression of six weeks' duration. The heart was a little enlarged to the left. The blood pressure was 152/84. An electrocardiogram showed right bundle branch block and prolonged A-V conduction. The P-R interval measured 0.22 second; the QRS interval was 0.11 second. There was no anemia. The diagnosis was coronary sclerosis.

Because of persistent epigastric discomfort, roentgenologic studies of the gastrointestinal tract were made. These showed carcinoma of the antral portion of the stomach. An operation was performed, and the patient died five days later of type III pneumococcus pneumonia. The organism was recovered in the blood culture.

An anoxemia test was done 2½ months before death, and was positive (Fig. 5).

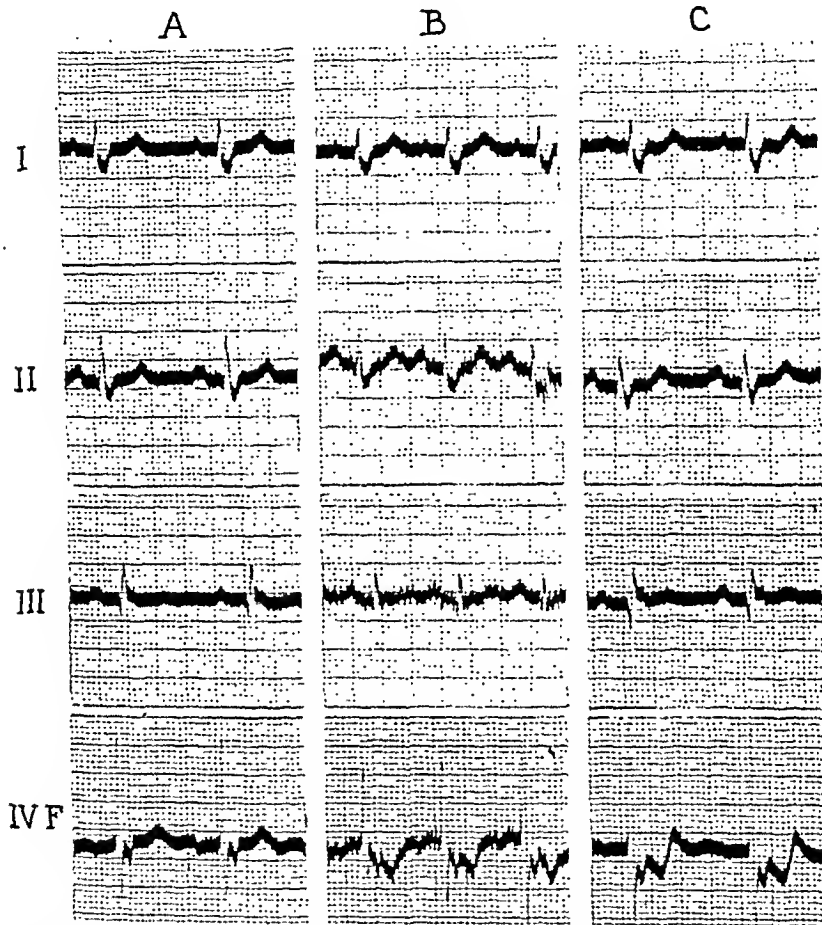


Fig. 5.—Case 1. Male, aged 67 years, had coronary sclerosis with precordial oppression for six weeks. Test was positive. Operation for carcinoma of stomach; death from pneumonia 2½ months after test. Necropsy showed narrowing of circumflex branch of left coronary artery and widespread fibrosis of posterior wall of left ventricle. A, Control. B, After ten minutes of anoxemia; pain. C, Immediately after one minute of 100 per cent oxygen.

*Necropsy.*\*—The heart weighed 400 grams. The walls of both coronary arteries showed numerous atheromatous plaques, without calcification. The lumen of the descending portion of the circumflex branch of the left coronary was narrowed to about half its normal size. There was widespread fibrosis of the posterior wall of the left ventricle. Elsewhere, the myocardium was free from scars. Microscopic examination of the left ventricle showed numerous, large areas of dense,

\*We are indebted to Dr. James W. Jobling, Director of the Department of Pathology, for permission to use the necropsy protocols.



fibrous, connective tissue. In these areas there were atrophy and disappearance of muscle fibers. Elsewhere, these fibers were normal. There was no cellular inflammatory reaction.

CASE 2.—E. P., Unit No. 453191. A white man, aged 61, had an attack of acute coronary occlusion in May, 1935, and remained in the hospital for six weeks. The electrocardiogram was characteristic of posterior myocardial infarction. He was followed in the outpatient department, where it was noted that his discomfort became progressively less. In October, 1937, he was taking only 2 nitroglycerin tablets each week.

In August, 1938, signs of congestive failure, with right-sided hydrothorax, appeared. The heart was enlarged. The blood pressure was 140/80. The electrocardiogram showed inversion of  $T_1$ ,  $T_2$ , and  $T$  in Lead IVF. He improved markedly with rest and therapy.

On Dec. 29, 1939, he was operated upon for carcinoma of the ascending colon. The operation lasted over three hours, and he stood it well. He died ten days later (Jan. 8, 1940) of peritonitis resulting from rupture of the intestinal anastomosis.

An anoxemia test, done three years after the attack of coronary occlusion and 8 months before death, was negative.

*Necropsy.*—The heart weighed 560 Gm. There were healed infarcts involving the left ventricle and interventricular septum. The coronary arteries showed advanced sclerosis, with occlusion of the anterior descending and circumflex branches of the left coronary by calcified material. Microscopically, at the apex of the left ventricle the wall was thinner than normal. There were no fresh areas of necrosis or inflammation. The small coronary arteries were slightly sclerotic and narrowed. The wall of the left ventricle showed similar changes. There were no recent thrombi in any of the coronary vessels.

Acute, generalized, fibrinopurulent peritonitis and bilateral lobular pneumonia were the immediate causes of death.

#### DISCUSSION

Judging from the evidence presented, it appears that a positive anoxemia test is a sign of functional insufficiency of the coronary circulation. This term is used to mean that there is a disproportion between the need of the heart for blood and the ability of the coronary vessels to deliver an amount sufficient to meet this requirement. Such a disproportion may be brought about by any factor which diminishes coronary flow or increases the work of the heart. As with all bodily functions, there is a reserve in the coronary bed which can be drawn upon in case of need. Only when this has been exceeded do signs and symptoms of insufficiency become apparent.

The commonest cause of a diminished coronary reserve is disease of the coronary arteries; and, of these diseases, arteriosclerosis comprises over 90 per cent.<sup>19</sup> But there are other causes, also, such as syphilis of the aorta, with stenosis or occlusion of one or both coronary orifices; aortic stenosis or insufficiency; paroxysmal tachycardia; and anemia, in which the heart suffers from anoxemia along with the rest of the body. In this paper only cases of coronary sclerosis have been discussed. Other conditions are being studied.

The usefulness of the test as a clinical diagnostic measure can best be illustrated by presenting briefly the following history:

CASE 3.—*Coronary sclerosis suspected. Pain atypical. Test positive.*

G. A. M., a male merchant, aged 53 years, complained of substernal pain of ten days' duration. His father died at the age of 65 of heart disease; his mother was over 90 years old. His health had been excellent. He was a hard worker, with large business responsibilities, and took almost no exercise. He smoked sixty cigarettes and drank four cups of coffee daily. His family physician had requested an electrocardiogram two years previously because he suspected that the patient had a "tired heart."

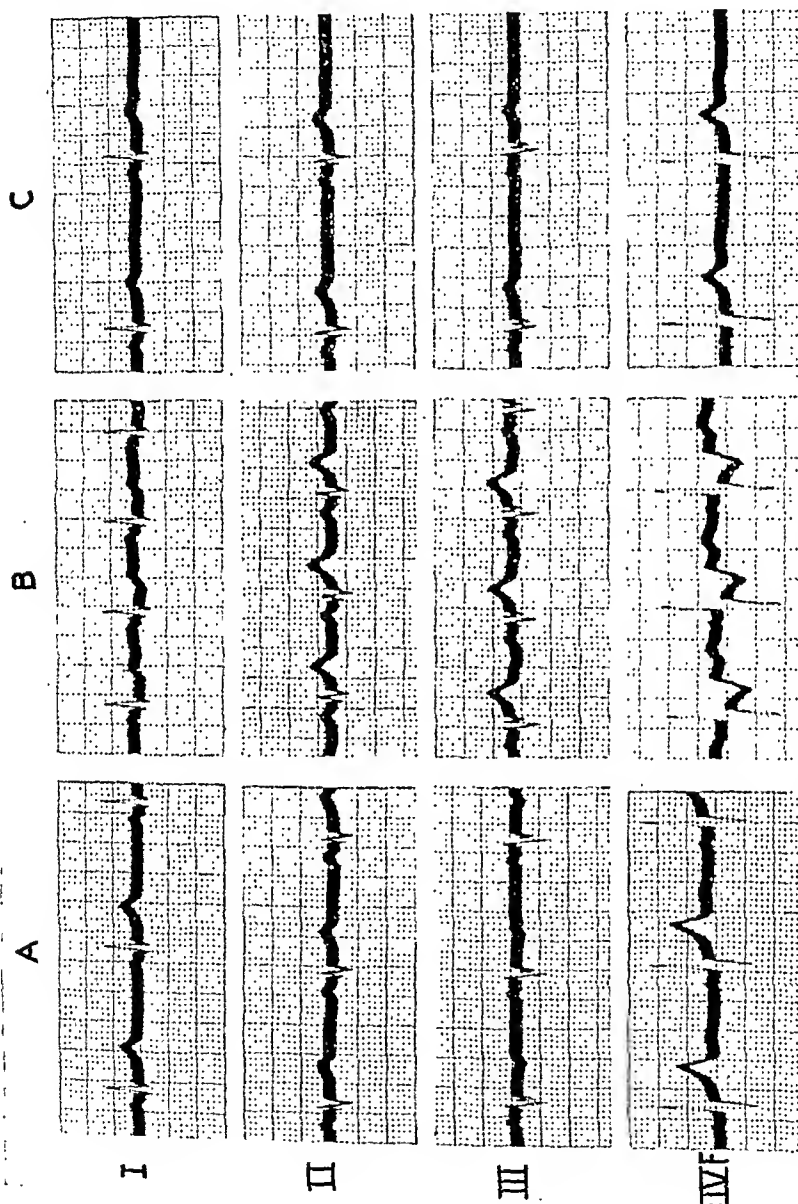


Fig. 6.—Case 3. Male, aged 53 years. Coronary sclerosis suspected; examination negative. Test was positive. A, Control. B, After ten minutes of anoxemia; pain. C, After one minute of 100 per cent oxygen.

Ten days before his visit he began to experience substernal pain which radiated to the back of the neck and to both arms, and usually occurred in the middle of the night. This recurred at intervals, and, according to his story, was unaffected by nitroglycerin. There was no discomfort during the day's activities. There was no dyspnea.

Examination showed that he was not overweight. There was no retinal or peripheral sclerosis. The heart was normal in size, as shown both by percussion

and orthodiagraphic measurement. The rhythm was normal, the rate, 64. The sounds were normal and clear. The blood pressure was 132/80. The electrocardiogram showed only left axis deviation.

It was the impression of the examiner that the patient suffered from nervous tension, as well as from poisoning by coffee and tobacco. He appeared to need a vacation. The anoxemia test was strikingly positive (Fig. 6).

He was seen again six months later. He was working less, and, on two evenings a week, retired at 6 o'clock, taking supper in bed. The discomfort continued at night for a time, but gradually became less marked. He noted upper sternal pressure on walking home from business, although there was no discomfort in the mornings when he was not tired. Emotional reactions also caused pain. Nitroglycerin, he now reported, gave relief. The electrocardiogram at this time was similar to the one taken previously.

He reported again eleven months after the first visit and stated that he was greatly improved. There was still some discomfort on walking when he was tired. Also, occasionally, after a heavy dinner, he had slight pain in the chest which radiated down the left arm. He required nitroglycerin rarely and irregularly, going sometimes for several months without it. During the entire eleven months, he took a capsule containing 3 grains of aminophyllin and  $\frac{1}{4}$  grain of phenobarbital three times a day.

The control electrocardiogram at this time was similar to those taken previously, except that the T wave in Lead III was upright. The anoxemia test was negative.

In this case, objective evidence of coronary sclerosis, obtained by the test ten days after the onset of symptoms, made possible a definite diagnosis. As a result of material modification in his mode of life there was progressive improvement. Increase in the functional capacity of the coronary circulation was demonstrated by the anoxemia test.

The test has also been used to follow the healing of an area of infarction. The electrocardiographic pattern gives a graphic picture of the development of an adequate collateral circulation, even when the control electrocardiogram remains unchanged. The following case is illustrative.

*CASE 4.—Coronary occlusion with cardiac infarction, followed by gradual lessening of symptoms. As the clinical condition improved, the anoxemia test, which was at first positive, became negative.*

W. T. D., Unit No. 568485. A male post office employee, aged 48 years, was admitted to the hospital March 18, 1939, complaining of attacks of substernal pain for one week. Two years previously he had been in bed for a month with what was called myocarditis. He had since had occasional, mild, substernal pain, which was unrelated to effort or meals. Nine days before admission he suffered an attack of substernal oppression which lasted two days, this time with radiation to the neck, left shoulder, and arm, and accompanied by syncope, nausea, and vomiting.

The clinical picture was typical of coronary occlusion. The electrocardiogram showed prolonged conduction, with a P-R interval of 0.33 second;  $T_1$  and  $T_2$  were inverted, and  $Q_3$  was large; these changes indicated posterior infarction. There was fever for a week. The erythrocyte sedimentation rate returned to normal on the eighth day after admission. Convalescence was uneventful.

Three months after the attack a teleroentgenogram showed a slight increase in the transverse diameter of the heart. He was having twinges of pain on effort. Five months after the attack there was still some heaviness in the precordium when he first went out in the morning. The blood pressure was 120/80. The anoxemia test at this time was positive (Fig. 7, A and B). There was gradual improvement,

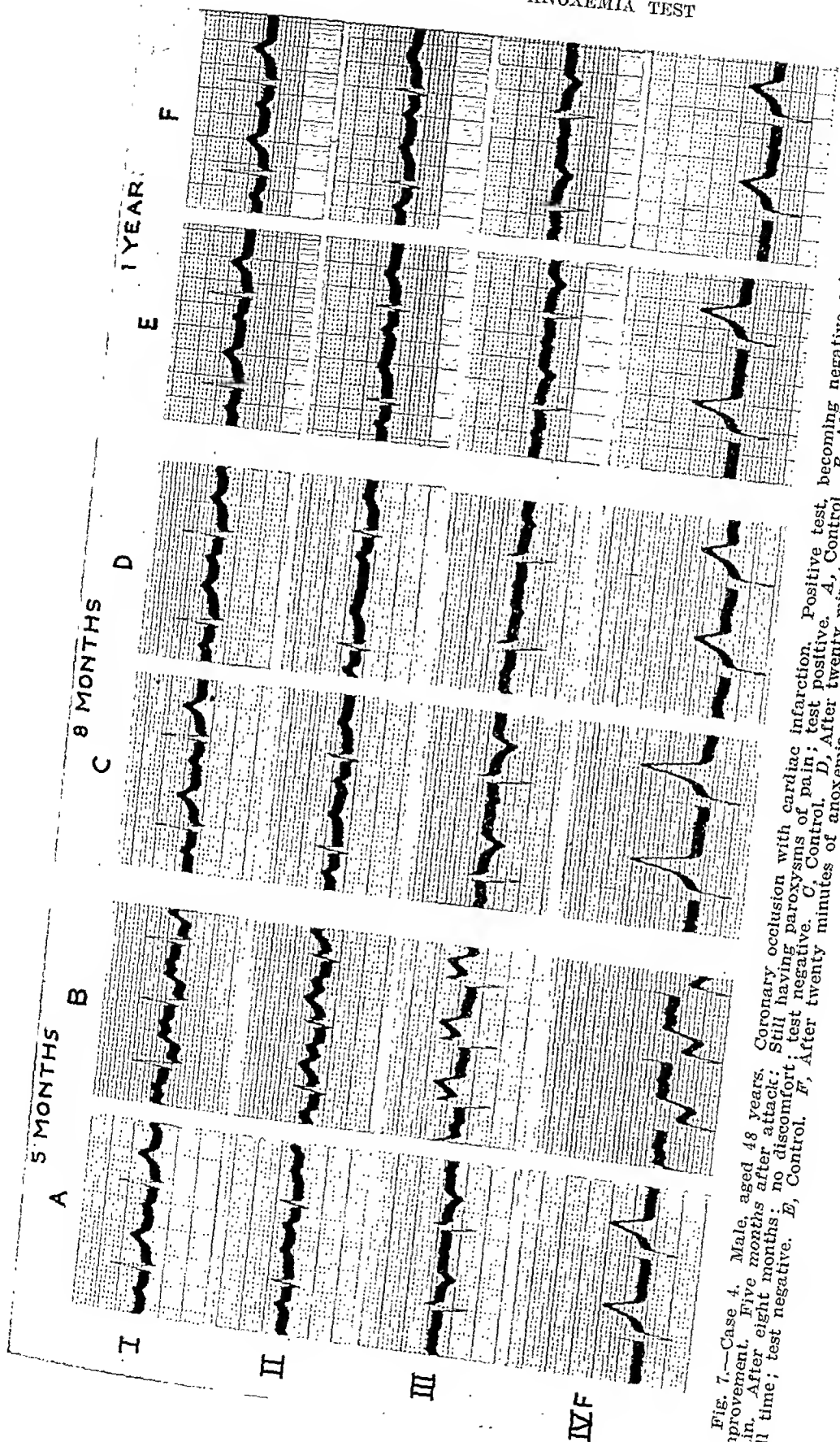


Fig. 7.—Case 4. Male, aged 48 years. Coronary occlusion with cardiac infarction. Positive test, becoming negative coincident with clinical improvement. Five months after attack: Still having paroxysms of pain; test positive. *A*, Control. *B*, After eighteen minutes of anoxemia; full time; test negative. *C*, Control. *D*, After twenty minutes of anoxemia; no pain. *E*, Control. *F*, After one year; working

with disappearance of all discomfort at the end of eight months. At this time the anoxemia test was negative (Fig. 7, *C* and *D*). A year after the attack of coronary occlusion he was working full time at his old job and had no complaints. The blood pressure was 125/70 (Fig. 7, *E* and *F*).

It is apparent (Table III) that, in a considerable number of cases, a negative test was obtained when symptoms and signs suggested the presence of coronary sclerosis. In some of these cases, later tests, taken when the pain was more frequent and intense, gave a positive result. In three cases, in all of which there were healed infarcts of the myocardium, both positive and negative tests were obtained at different times, within a few months, without demonstrable change in the clinical status. The explanation for this is not entirely clear, but it is possible that in such cases the margin of coronary reserve is small; relatively slight factors, such as emotional upsets, indigestion, or an added burden of work, may suffice, on occasion, to decide the balance. Probably, also, organic changes which are not accompanied by symptoms occur in the coronary circulation from time to time. One patient with a typical history of anginal pain, but with a negative physical examination and anoxemia test, suffered an attack of coronary occlusion eleven months after his visit to the clinic. This was an instructive experience and is here briefly told.

CASE 5.—A. W., Unit No. 409247. The patient was a plumber, aged 43 years. His symptoms had begun six months previously (July, 1938), with pain in the precordium and dyspnea on exertion. He had never been seriously ill. The pain began with a feeling of pressure under the sternum and radiated to the left axilla. There was progressive shortness of breath on effort.

Percussion showed that the heart was normal in size. The sounds were loud and clear. The blood pressure was 128/74. A teleroentgenogram showed a slight increase in the cardiothoracic ratio. The blood cell count was normal. The Kline test on the blood was negative. An electrocardiogram showed left axis deviation;  $T_3$  was inverted;  $R-T_1$  was slightly elevated; and the precordial lead was normal. An anoxemia test on March 22, 1939, was negative. Shortly after the start of the test the patient complained of mild retrosternal pressure, and, at the end of eighteen minutes, experienced slight pain. However, this disappeared quickly, and he completed the full twenty minutes of anoxemia. He stated that the discomfort was similar to that which occurred spontaneously, and was accompanied by slight nausea.

He was followed in the outpatient clinic, and was thought to be able to do ordinary work. On Jan. 15, 1940, he had an attack of acute coronary occlusion, according to his physician. An electrocardiogram which was made at the Presbyterian Hospital on Feb. 26 (six weeks later), confirmed the diagnosis;  $T_2$  was diphasic and  $T_3$  and  $T$  in Lead IVF were inverted. The erythrocyte sedimentation rate at this time was 15 mm. in one hour.

There are at least five reasons why there may be a discrepancy between the clinical diagnosis and the result of the anoxemia test: (1) The clinical diagnosis was incorrect. (2) The criteria employed were sufficiently rigid to exclude borderline cases. (3) The area of the heart affected by

the coronary lesions was "silent" with respect to electrocardiographic changes caused by anoxemia. Following infarction of the lateral wall of the heart, the resting electrocardiogram may show only minor and transitory alterations in form.<sup>20</sup> (4) The coronary lesions were early and slight; the coronary flow was not reduced sufficiently to register changes under the conditions of the test (Case 5). Larsen<sup>8</sup> has called attention to cases in which there were a negative anoxemia test and a positive reaction to exercise. (5) After infarction, an adequate collateral circulation may be established, so that, actually, coronary insufficiency does not exist<sup>21</sup> (Cases 2 and 4).

It is apparent, then, that a positive anoxemia test is a sign of coronary insufficiency and indicates a *diminished coronary reserve*. So far, no other clinical condition has been found to be associated with similar changes in the electrocardiogram. A negative test, however, does not exclude the presence of coronary lesions or of a healed myocardial infarct.

The test is simple and safe. It has proved to be of diagnostic value in distinguishing pain of coronary origin from that due to other causes. It has been employed to study, in patients, the effect of various drugs on the coronary circulation. It affords a graphic method of recording the efficiency of the coronary circulation at varying intervals after coronary occlusion. It is suggested that it may be employed as a measure of the effectiveness of the establishment of collaterals in the coronary bed after surgical procedures designed to promote their formation. It should prove useful in the examination of patients who claim disability benefits because of anginal pain, and in insurance examinations when coronary sclerosis is suspected. Only a positive result should be regarded as significant.\*

#### SUMMARY

1. Using an apparatus and a technique previously described, anoxemia tests were performed on 115 normal persons and 147 patients with suspected or manifest cardiac disease. In all, 326 tests have been carried out on 262 subjects, in the course of which 2,316 electrocardiograms were taken.

\*Since this paper was written and presented, Riseman and his collaborators have reported their experience with "electrocardiographic changes during generalized anoxemia as a diagnostic criterion of angina pectoris or coronary artery disease" (Riseman, J. E. F., Waller, J. V., and Brown, M. G.: *The Electrocardiogram During Attacks of Angina Pectoris; Its Characteristics and Diagnostic Significance*, AM. HEART J., 19: 683, 1940). Observations were made on five patients with angina pectoris and eight normal subjects, who were allowed to breathe an atmosphere containing "approximately" 10 per cent oxygen for ten minutes, or until pain was felt. There were no untoward effects. Only the precordial lead was used, and in each group this was recorded by a different technique. In the patients with angina the tracings were taken according to the old method, using the apex and left arm; in the normal subjects, they were taken according to the newer technique, using the apex and right arm (Lead IVR). Accurate comparison between the two sets of records was obviously impossible. It was concluded that "changes in the electrocardiogram during generalized anoxemia appear to be of little practical value in differential diagnosis, for the difference between the normal and abnormal responses is not sufficiently marked to avoid serious error; and that, judging from the literature, the induction of generalized anoxemia is not without danger." In view of the limited number of observations and the manner in which these were carried out, further comment is unnecessary. The questions raised by the conclusions are answered fully in the body of our paper.

2. In normal persons, the changes in the form of the electrocardiogram during anoxemia are relatively slight. There is usually lowering of the amplitude of the T waves in all of the four leads. There may be inversion of the T wave in Leads II and III.

3. Criteria have been established for an abnormal response. These criteria are sufficiently rigid to exclude alterations in the form of the electrocardiogram which may occur as the result of emotion or other spontaneous variables.

4. The test was positive in 18 per cent of 33 patients with suspected coronary sclerosis; in 31 per cent of twenty-two patients with coronary sclerosis but no history of anginal attacks; in 55 per cent of seventy-three patients with coronary sclerosis and a history of anginal attacks; and in only 5 per cent (one case) of nineteen patients with hypertension without symptoms or signs of coronary sclerosis. Patients whose control electrocardiogram was abnormal showed a higher percentage of positive tests than those with a normal control tracing. The highest incidence of positive tests was obtained in a group of forty-nine patients with anginal pain caused by coronary sclerosis and abnormal control electrocardiograms; in 69 per cent of these an abnormal response was obtained.

5. There was no relationship between the size of the heart and the incidence of positive tests.

6. There was no constant effect on pulse rate and blood pressure.

7. There was no constant relationship between the occurrence of a positive test and the appearance of pain during anoxemia.

8. No serious untoward effects were observed, provided the test was not carried out when congestive failure was present, was not done more than once on the same patient within twenty-four hours, and was not made before the lapse of four months after an attack of coronary occlusion.

9. Unpleasant reactions were encountered twenty-four times in seventeen cases. These were classified as vasovagal attacks, convulsions, hyperventilation, dyspnea, and mental confusion. None of these reactions was serious or harmful.

10. Nine of the patients in the group died at varying intervals following the test. Necropsies were performed on two. In one case in which the test had been positive, narrowing of the circumflex branch of the left coronary artery and widespread fibrosis of the posterior wall of the left ventricle were found. The heart of the second patient, who had had an attack of coronary thrombosis 5 years before his death from post-operative peritonitis, showed old occlusion of the anterior descending and circumflex branches of the left coronary artery, with healed infarcts of the heart. In this case, the anoxemia test, done eight months before death, was negative.

11. A negative test does not rule out the possibility of early coronary lesions or of healed cardiac infarction. Some of the reasons for the high incidence of negative tests in cases of suspected or known coronary sclerosis have been discussed.



12. The test is simple and safe. When positive, it is a sign of coronary insufficiency and indicates a diminished coronary reserve.

13. The test has proved to be of diagnostic value in distinguishing pain of coronary origin from that due to other causes. It has been useful in affording a graphic record of the efficiency of the coronary circulation at varying intervals following coronary occlusion. It has afforded a method for studying, in patients, the effect of various drugs on the coronary circulation.

14. It is suggested that it may be employed as a measure of the effectiveness of the establishment of collaterals in the coronary bed following surgical operations designed to promote their formation.

15. It may prove useful in cases in which disability is claimed because of anginal pain, and also in insurance examinations when coronary sclerosis is suspected.

16. Only a positive result should be regarded as significant.

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#### DISCUSSION

DR. CLOUGH T. BURNETT (Denver).—I want to congratulate Dr. Levy on his paper and his very excellent slides. In Denver, my associates and I have been much interested in this subject. We felt that it was worth while to repeat Dr. Levy's work for two reasons. We live at an altitude of a mile above sea level, and felt that this might have a profound effect upon the results of the test because, in the earlier work of Dr. Levy, age was not given so much consideration.

We have done more than 120 tests. Most of these were on normal young adults between the ages of 20 and 40 years, but a few of the subjects were more than 40 years old.

Our criteria for the normal (and we have attempted so far as possible to work with the normal) have been essentially those of Dr. Levy.

We have noted some points that are of interest. For example, we have checked the pulse pressure, which was not mentioned this morning by Dr. Levy, but was in an earlier paper. We do not feel that these changes can be considered significant, and, in all of the tests, such changes as we have encountered contradict the contention that this test involves an undue strain on the subject.

All of those associated in this investigation have taken the test several times, but never twice on the same day. One of us has taken it four times. Under proper control we consider it safe.

We noticed progressive cyanosis of the fingertips. We would like to work out some means to standardize this. So far we have not. During the first few minutes of the test there is moderate air hunger, which shortly disappears. Any tendency to fear at the beginning naturally gives false control blood pressure and pulse rate levels, and this is misleading because these values may be lower at the end of the test than before it was begun.

Dr. Levy mentioned some unpleasant experiences. We had two such experiences on the same day, and, unfortunately, with two of our older colleagues. We found that this was caused by an unrecognized error in the composition of the oxygen-nitrogen mixture. In this case we were working with an 8.6 per cent oxygen content, which is too low for safety. These subjects found that the test was intolerable, and it had to be discontinued.

Dr. Levy mentioned syncope. As I understood him, he said that it hadn't occurred. We had two cases of apparent syncope on the same afternoon, with a marked reduction in the pulse rate and blood pressure. Since both of these occurred in women, and the second subject had seen what happened to the first, we regarded it as psychic in origin. These were the only occurrences of this kind in approximately 120 tests.

We found that physicians and nurses were the poorest subjects, probably again for psychic reasons. We have found, also, that giving too elaborate instructions to the subject regarding the test is probably undesirable.

There is a remarkable uniformity in the electrocardiographic pattern at the age with which we have worked. As to the older subjects, I would not care to make any comment at this time.

Dr. Levy mentioned mental confusion. We have encountered this in two instances, and one of these two subjects nearly had a convulsion. In all of these instances the undesirable effects were controlled immediately with the pure oxygen which, of course, must be available for emergencies.

Of peculiar interest to physicians who practice in the higher altitudes is the response of normal persons who have lived at sea level and travel to higher altitudes. We have made some observations on such subjects and hope to have sufficient additional observations in a few months. The usual control observations are made at sea level. Fortunately, there are two trains which run from Chicago to Denver in fifteen hours, so that the ascent of practically one mile is made in this time. Immediately on arrival the second set of observations is made, and at once the subject is taken to the highest possible altitude. In winter we have used Berthoud Pass, which has an altitude of 11,306 feet; in summer we plan to go to the summit of Mt. Evans, which is 14,260 feet above sea level. At these mountain stations a third series of observations is made, after which oxygen is administered for one minute, as in the standard test, and a fourth series of clinical and electrocardiographic records obtained. Naturally, this series is small, and we do not care at this time to make any detailed statement, but the effect of rapid change in altitude appears to be quite similar to that of artificially induced anoxemia.

At this time I wish to express our appreciation for the courtesies and cooperation extended to our group by Dr. Levy.

Dr. H. R. MILLER (New York City).—I, too, found it a pleasure to hear Dr. Levy. I wonder whether he would be good enough to reconcile his results with some experimental data which we published a number of years ago, and with certain physiologic criteria which bear upon the same problem.

Together with Drs. Felberbaum and Krigel, we obtained, in healthy cats, electrocardiographic changes similar to those shown by Dr. Levy. These effects were caused by asphyxia, and they disappeared when the cats were allowed to recover.

These and similar observations raise the point whether one is dealing fundamentally with a chemical process or a nervous regulation. The possibility that there is a nervous regulation is related to the investigations of Levy, in England, and to the studies of Beattie, Brow, and Long, who demonstrated that, in cats, cardiac arrhythmias may be induced (and registered electrocardiographically) merely by putting the cat under chloroform. The effects were abolished when the efferent sympathetic fibers which descend from the diencephalon were severed. In other words, although a chemical agent, in this instance, chloroform, still acts, or, at least is still expected to be in operation, the induced effect upon the cardiac mechanism can be abolished by interrupting a nervous pathway.

Another point which seems to me of some interest revolves about any inference that blood flow (with reference to the heart, the quantity of blood received by this organ) is synonymous with the oxygen content or saturation. As far as I know, the level of oxygen concentration of the blood does not parallel the level of blood pressure in the sinuses of Valsalva. It is therefore quite conceivable that the quantity of blood which the heart will receive, under adverse circumstances or in emergencies, may be entirely adequate and the oxygen content deficient, or vice versa.

The latter point, I believe, is tied up with the important physiologic consideration that in all circumstances when the heart is threatened, whether by shock or asphyxia, or whether the coronary vessels themselves are damaged, the physiologic equilibrium of cardiovascular dynamics operates to bring more blood than ever

to the heart. This has some relevancy not only to the aspect of the nervous regulation of the circulation, especially of the coronary circuit, but is significant in the light of the recent studies of the Albany workers, Martin and Gorham. They showed that the amount of blood which can enter the irrigating vessels of the heart may be more than normal when, for example, a coronary vessel is pulled upon tridirectionally and pain is produced.

The final query I wish to bring up is whether it would not be of advantage, certainly from a clinical point of view, to separate the effects of asphyxia from those initiated as electrocardiographic changes. These two sets of effects need not be concurrent.

DR. LOUIS N. KATZ (Chicago).—Would Dr. Levy tell us how many normals there were in the older age group, i.e., those approaching senescence, as compared with the younger group? Secondly, would he use this test in preference to his own clinical judgment?

We had the good fortune to have with us M. Kissin, who, several years ago, with M. A. Rothschild, initiated the use of anoxemia as a test for angina pectoris. In collaboration with Drs. Hamburger and Schutz, Dr. Kissin and I gave the foregoing method a further trial on normals and patients with coronary disease; we were soon convinced that it was potentially too hazardous for general use, and that the distinction between normals and patients with coronary disease who had normal electrocardiograms to begin with was not always marked.

DR. ROBERT L. LEVY (New York).—I greatly appreciate Dr. Burnett's interesting discussion. Our observations on changes in blood pressure and heart rate, like his, have shown no direct relationship to the outcome of the test, that is, as to whether it was positive or negative. We have checked our oxygen mixture at frequent intervals and have found that it did not vary more than plus or minus 0.6 per cent.

Fear, it is known, causes changes in the form of the electrocardiogram. We have observed changes in normal persons during the first test which did not appear during the second. Our criteria have been made sufficiently rigid so that the changes caused by fear are covered by the range of normal variation.

Dr. Miller has referred to the mechanism of the action of anoxemia and asphyxia. I cannot take time to go into that here. It has been shown, notably by Gellhorn and his associates, that anoxemia affects both vagus and sympathetic systems, and these workers have, quite recently, published an interesting monograph on the effects of anoxia and asphyxia on the vasomotor system.

As Dr. Miller has pointed out, pain and a positive test are not necessarily associated. A positive test may be obtained without the appearance of pain, and vice versa. Sometimes both occur.

As for Dr. Katz's points, in the first place, the test that Kissin and Rothschild used was not comparable to the one we employed. I think that should be made very clear. Their patients rebreathed the same mixture; and with that method no standardization of the results is possible.

In the second place, he asked how many normals showed a positive test. Of course, no normals showed a positive test because our criteria were made up on the basis of the range of variation observed in people without heart disease.

He asked also whether it is feasible to use the test in private practice. I use it in my own office. One of the patients whose tracings were shown, in my opinion, did not have coronary sclerosis. You will recall that the physical examination and the control electrocardiogram were negative. I thought that he was working too hard, smoking too much, and going to too many night clubs. Because his test was positive, he was advised to modify radically his mode of life. His improvement, in the course of a year, was striking.

## EXPERIMENTAL ATHEROSCLEROSIS

### III. ELECTROCARDIOGRAPHIC STUDIES AND PATHOLOGIC CHANGES IN THE HEARTS OF CHOLESTEROL-FED RABBITS

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SINCE atherosclerosis was first produced experimentally about twenty-five years ago in rabbits by the feeding of cholesterol, an appreciable amount of work on the pathologic and chemical phases of the problem has been carried out in this country and abroad. As far as is known, however, there are no studies relating experimental atherosclerosis of the coronary arteries with electrocardiographic changes. An investigation of this kind appeared all the more important since clinical studies of patients with heart disease have emphasized the frequent association of coronary artery disease and abnormal electrocardiograms.

#### MATERIAL AND METHODS

Twelve rabbits varying in age from 3 to 4 months were obtained. Five were set aside as controls and were observed for 126 days. Purina chow was fed once daily, and water was left in the cages at all times. To the same basal diet of each of seven rabbits was added 1 Gm. of cholesterol three times a week. This group was also studied for 126 days. Electrocardiographic studies and blood cholesterol determinations were carried out at intervals of two to five weeks. The electrocardiographic studies included the usual standard leads, as well as exploratory leads from the right (V) and left (IV) chests paired with an indifferent electrode on the left thigh.

The cholesterol content of the whole blood was determined by a modified Bloor procedure.<sup>1, 2</sup> The method of sacrificing the animals and the technique for removal of the aorta and for the determination of its cholesterol content have been described elsewhere.<sup>3</sup> At necropsy, several sections were taken from the heart for microscopic study.

#### RESULTS

*Blood Cholesterol.*—The whole blood cholesterol of the control rabbits on the 126th day of observation ranged from 120 to 200 mg. per cent, and that of the cholesterol-fed rabbits from 280 to 1,210 mg. per cent (Table I).

*Body Weight.*—In 126 days the control rabbits gained from 255 to 636 Gm. in weight, and the experimental rabbits from 113 to 1,641 Gm. (Table I).

*Cholesterol Content of the Aorta.*—The cholesterol content of the aorta in the control rabbits ranged from 0.402 to 0.588 Gm., with a mean of 0.465 Gm. per 100 Gm. of dry aorta. The cholesterol content

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TABLE I

WHOLE BLOOD CHOLESTEROL, CHOLESTEROL CONTENT OF THE AORTA, GAIN IN BODY WEIGHT, PATHOLOGIC OBSERVATIONS OF AORTA AND HEART, AND ELECTROCARDIOGRAPHIC CHANGES IN CONTROL RABBITS AND IN RABBITS RECEIVING 3 GM. OF CHOLESTEROL A WEEK FOR 126 DAYS

RABBIT NO. AND SEX	BLOOD CHOLESTEROL (MG. %)					TOTAL GAIN IN WEIGHT (GM.)	AORTA CHOLES- TEROL (GM. PER 100 GM. DRY WEIGHT)	PATHOLOGIC OBSERVATIONS		ELECTROCARDIOGRAPHIC CHANGES*		
	0 DAYS	15 DAYS	44 DAYS	85 DAYS	126 DAYS			MACROSCOPIC (AORTA)	MICROSCOPIC (HEART)	RATE	QRS VOLTAGE IN INDICATED LEADS	T VOLTAGE IN INDICATED LEADS
Control Group												
12, M	101	116	125	109	131	636	0.437	Apparently normal	Coronary arteries and myo- cardium without alteration	Decreased	Decreased II, III	No change
13, F	97	123	154	109	120	425	0.424	Apparently normal	Coronary arteries and myo- cardium without alteration	Increased	Decreased II, III, IV, V	Indeterminate
14, M	120	142	160	117	184	340	0.402	Apparently normal	Coronary arteries without al- teration. Myocardium, lym- phocytic foci in lateral ven- tricular wall	Decreased	Decreased I, V Increased III, IV	Decreased IV Increased I, II, III, V
15, F	128	188	200	204	200	623	0.473	Apparently normal	Coronary arteries and myo- cardium without alteration	Decreased	Decreased I, II, III, IV, V	Increased V from nega- tive to posi- tive
16, F	114	108	170	156	144	255	0.588	Apparently normal	Coronary arteries and myo- cardium without alteration	No change	Slightly decreased I, II, III	Decreased IV from positive to negative
Cholesterol-Fed Group												
1, F	128	335	938	721	833	1585	7.610	Marked athero- sclerosis	Atherosclerosis of coronary arteries (interauricular and interventricular septa, left posterior papillary muscle, valvular apparatus). Myo- cardium without alteration	Increased	Decreased I, II, III	No change

\*The P-R and QRS intervals, the electrical axis, and the RS-T segment remained unchanged throughout in both control and cholesterol-fed rabbits.

3, M	101	109	361	251	280	538	1,217	Minimal athero- sclerosis	Atherosclerosis of coronary arteries (left auricle and ven- tricle, interauricular and in- terventricular septa). Myo- cardium without alteration	Decreased	Decreased I, II, III	No change
5, F	111	330	708	781	872	311	2,052	Moderate athero- sclerosis	Atherosclerosis of coronary arterioles and mitral valves (interventricular septum and auricular walls). Myo- cardium without alteration	Increased	Decreased II Increased I	Decreased III from isoelec- tric to nega- tive
6, M	108	494	636	721	765	198	2,233	Moderate athero- sclerosis	Atherosclerosis of coronary arteries (left auricular and left ventricular walls and great vessels). Myocardium without alteration	Increased	Decreased II, III, V	No change
9, M	127	361	636	695	765	1641	10,791	Marked athero- sclerosis	Atherosclerosis of coronary arteries (left ventricular wall and left anterior papillary muscle). Myocardium, focal myocarditis of the right auricle	Increased	Decreased I, II, III	Decreased V from positive to negative
10, F	112	361	833	551	507	454	7,568	Marked athero- sclerosis	Atherosclerosis of coronary arteries, larger and smaller branches (left anterior papil- lary muscle, auricular walls, and great vessels). Myo- cardium, areas of swelling and vacuolar degeneration	No change	Decreased I, II, III, V	Decreased IV, V
11, F	104	399	938	1072	1210	113	15,441	Marked athero- sclerosis	Atherosclerosis of coronary arteries (left anterior papil- lary muscle and interven- tricular septum). Myo- cardium without alteration	Decreased	Increased I, II, III	Decreased IV, V

of the aorta in the cholesterol-fed rabbits ranged from 1.217 to 15.441 Gm., with a mean of 6.701 Gm. per 100 Gm. of dry aorta (Table I).



Fig. 1.—Photomicrograph of section of heart of cholesterol-fed rabbit 9, showing two markedly atherosclerotic coronary arterioles and the normal myocardium. (H&E  $\times 170$ .)

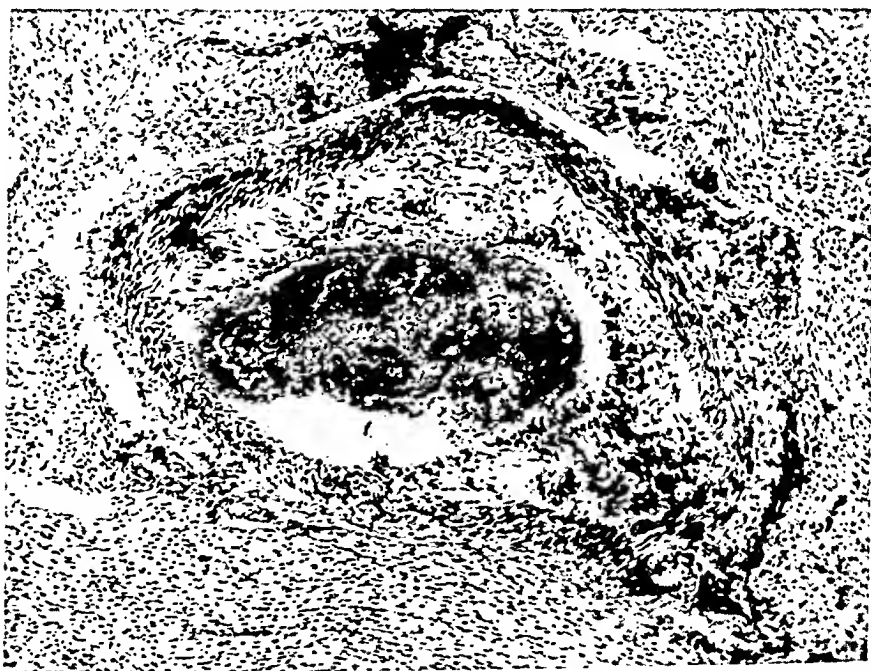


Fig. 2.—Photomicrograph of section of heart of cholesterol-fed rabbit 11, showing marked arteriosclerosis of a coronary artery. (H&E  $\times 130$ .)

*Pathologic Observations.*—On macroscopic examination, the aortas of the control rabbits appeared normal. The degree of atherosclerosis observed macroscopically in the cholesterol-fed animals paralleled very closely the cholesterol content of the vessels. On microscopic examina-

tion, the aorta, coronary arteries, coronary arterioles, and myocardium were essentially normal in the control rabbits. In the cholesterol-fed rabbits, marked atherosclerotic intimal thickening of coronary arteries and arterioles was present in each heart. A few scattered foci of lymphocytic infiltration of the myocardium (auricular or ventricular) were noted, and there were no changes indicative of myocardial degeneration or infarction (Figs. 1 and 2, Table I).

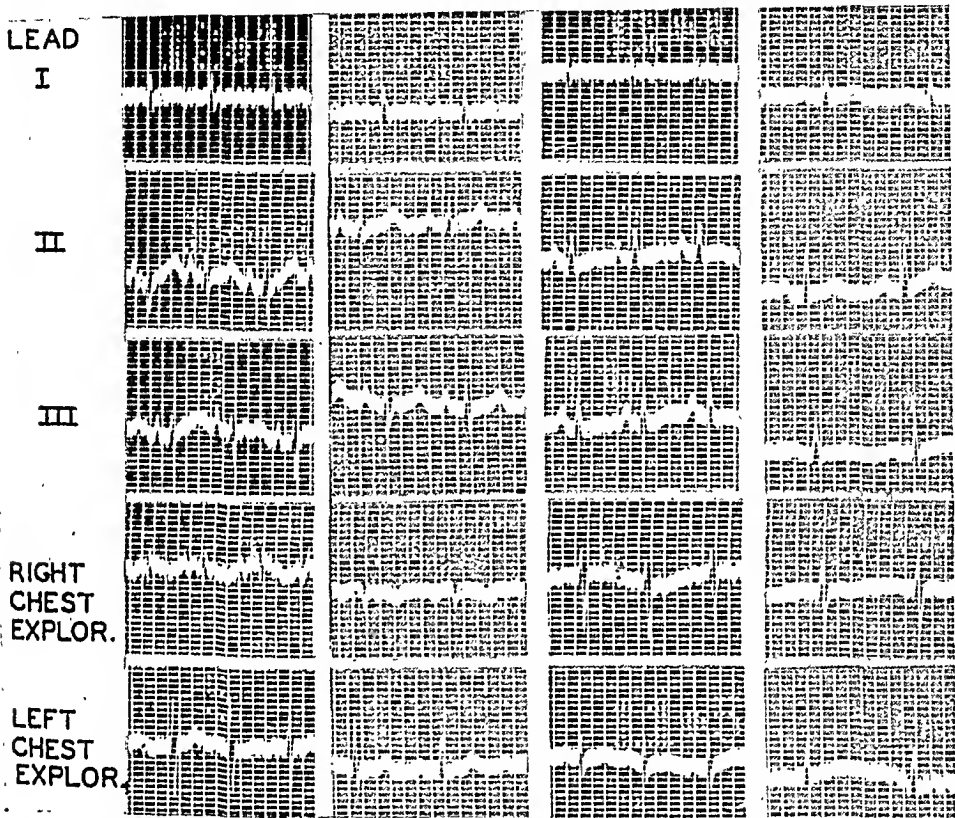


Fig. 3.—4, Electrocardiogram of control rabbit 12 on June 6, and B, electrocardiogram of same rabbit on October 11. (same year), showing only slight changes in the QRS and T waves. C, Electrocardiogram of cholesterol-fed rabbit 11 on June 6 prior to cholesterol feeding, and D, electrocardiogram of same rabbit on October 11 after four months of cholesterol feeding, showing minor changes in the QRS and T waves which are difficult to evaluate.

*Electrocardiographic Studies.*—No significant changes in the heart rates or in the electrical axis were observed in either the control or cholesterol-fed rabbits. The total voltage as judged by R or R plus S in Leads II and III appeared to decrease in both groups during the 126 days of observation; however, in the cholesterol-fed rabbits an increase in the voltage occurred within three to six weeks after cholesterol feeding was begun, but after this period the voltage returned rapidly to that of the control rabbits. No significant changes in the P-R or QRS intervals were observed in the experimental animals. The RS-T segment varied appreciably with the respiratory phase; however, no definite alterations were observed in the cholesterol-fed group. In



both control and experimental animals, the T waves were more subject to change in the exploratory leads than in the other leads; either no change, an increase, or a decrease characterized the unpredictable T wave direction. Extrasystoles occurred in both control and cholesterol-fed rabbits infrequently and were more often associated with slow heart rates (Fig. 3, Table I).

Levy and co-workers<sup>4</sup> recently reported alterations in the electrocardiograms of patients with coronary sclerosis during rebreathing of low oxygen mixtures. A control rabbit was made to breathe 10.5 per cent oxygen for twenty to thirty minutes, but only minimal electrocardiographic changes were noted as a result of this procedure. However, each of two rabbits with hypercholesterolemia induced by cholesterol feeding for a period of seven months showed a sharp decrease of the QRS voltage in Leads I, II, and III, and changes of the T wave in the exploratory leads during the administration of this low oxygen mixture.

#### DISCUSSION

Our results indicate that although marked narrowing occurs in coronary arteries and arterioles of rabbits fed cholesterol over a prolonged period of time, no evidence of myocardial degeneration or of significant electrocardiographic changes is observed.

In a limited study, it appears that on administration of gas mixtures low in oxygen, the nutrition of the myocardium is seriously affected in cholesterol-fed rabbits with the assumption, of course, that the electrocardiographic deviations observed are significant. These findings substantiate the conclusions of Wilson<sup>5</sup> that the activity of the coronary arteries themselves makes no recognizable contribution to the form of the electrocardiogram and the diseases of the arteries have no known effect upon the action currents of the heart, except so far as they temporarily or permanently alter the blood supply to some portion of the myocardium.

#### CONCLUSIONS

Although coronary arteries and arterioles of rabbits fed cholesterol over a prolonged period of time showed pronounced atherosclerosis, no evidence of structural change in the myocardium or of significant alterations in the electrocardiogram was observed. In a limited study it appeared that, as a result of the atherosclerotic vascular narrowing, the nutrition of the myocardium was seriously affected in cholesterol-fed rabbits, as revealed by electrocardiographic studies during the rebreathing of gas mixtures low in oxygen.

Grateful recognition is given to Marcella F. Hughes and Beatrice Tanney, B.A., for aid in taking the electrocardiograms; to Samuel Member, B.S., and Sylvia Ehrlich, B.A., for their help in the chemical studies; and to Julius Wilensky, B.S., for general assistance.

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## A NEW CLAMP FOR THE GRADUAL OCCLUSION OF CORONARY ARTERIES

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BECK and his associates in 1932 demonstrated in dogs the presence of blood vascular connections between the myocardium that had been intentionally rendered ischemic and an onlay graft of pectoral muscle.<sup>1</sup> Feil and Beck<sup>2</sup> applied this principle of collateral circulation to human patients suffering from myocardial ischemia due to coronary arteriosclerosis. Because of this work considerable impetus has been given to the study of surgical methods for augmenting the blood supply to the myocardium. The myocardial ischemia was effected in the original animal experiments by successively closing a silver U-shaped clamp at repeated operations. Since that time studies in this laboratory by Beck, Mautz and Thornton and elsewhere by others have given rise to a number of ingenious devices for effecting this coronary artery occlusion, the aim of each being gradual occlusion to simulate that occurring in coronary arteriosclerosis. The most widely used clamps operate on the principle of the screw, being fractionally closed in multiple stages at a rate found practical by experience, usually requiring three or more stages and attended by high operative mortality. To avoid the necessity of reopening the chest each time further closure was desired, Thornton and Mautz<sup>3</sup> in this laboratory and Blum, Schauer and Calef<sup>4</sup> in New York extended the screw-arm to an easily accessible subcutaneous position. All of these clamps, however, share the objectionable feature of permitting only periodic abrupt increase in closure rather than a continuously progressive closure which so often occurs in coronary arteriosclerosis.

A clamp is here described which, utilizing the principle of osmosis, effects gradual arterial closure at a fixed rate by the swelling of a contained charge of hypertonic solution. The clamp (Fig. 1B), constructed of pure silver, is approximately 2.5 cm. long. It is composed of a cylindrical barrel (*a*) which holds the hypertonic charge. On the anti-arterial end it is closed by a semipermeable membrane of measured porosity (*b*), held in place by a perforated screw-top (*c*), and on the other (arterial) end an L-shaped extension (*d*) holds the artery which is compressed by a piston (*e*) moved by the swelling hypertonic charge

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(f). The open limb of the L-shaped end is closed by means of an arm on a sliding cuff (g), thus holding the artery (h) in place within the clamp during occlusion. In order to prevent leakage of hypertonic charge, a thin latex rubber bag (2) is fitted into the clamp, as shown in Fig. 1 C and D, employing double metal washers (1 and 3).

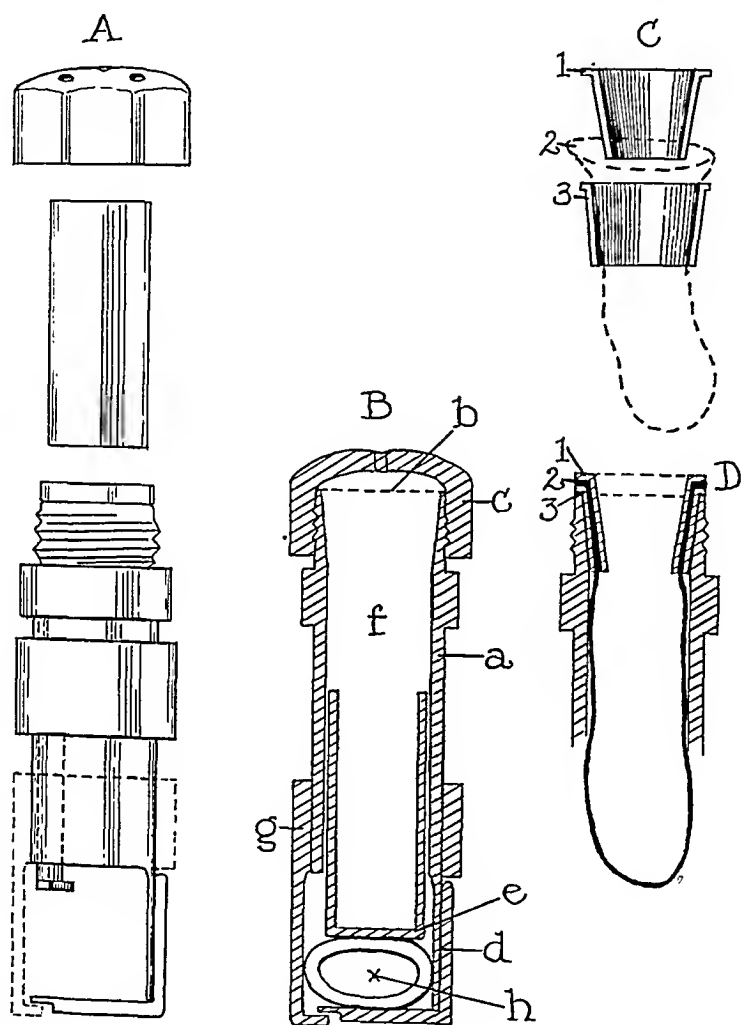


Fig. 1.

The rate of increase in volume of the hypertonic charge, and therefore the rate of closure of the clamp, is a function of two variables: (1) membrane porosity, and (2) solution (charge) concentration. The membranes used in this work are prepared after the method described by Elford,<sup>5</sup> yielding a tough membrane of uniform porosity. With a 100 per cent sucrose charge, membranes have been used in this work that have closure periods varying from 48 hours to 60 days. Less permeable and therefore slower closing membranes can be made but have not yet been used. The hypertonic charge employed has been 100 per cent sucrose solution, which possesses two advantages: (1) because

of high viscosity the possibility of pressure leaks within the clamp is minimized, and (2) the osmotic pressure developed is high.

Arterial closure with this clamp is done most advantageously because: (1) Only one surgical procedure is required; (2) arterial constriction progresses at a constant rate, though slowing up terminally because of charge dilution; (3) any desired rates of closure within wide limits can be provided by control of membrane porosity and charge concentration. The results of the use of this clamp will be presented in a later publication. We have used it in obtaining satisfactory gradual closure of the coronary arteries, the abdominal and thoracic aortae, and the pulmonary and renal arteries. It is suggested that this clamp will find use in the study of occlusion effects of other arteries. Clinically it might be employed to occlude large arteries slowly when acute occlusion is hazardous.

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## Department of Clinical Reports

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### A CASE OF BACTERIAL ENDOCARDITIS ILLUSTRATING THE MECHANISM OF LOCALIZATION AND THE NATURE OF VEGETATIONS

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IN A recent paper<sup>1</sup> the general principles of a concept of the mechanism of the localization of vegetations were outlined. Briefly, this concept is based on laws of hydrodynamics and states, in effect, that vegetations occur primarily at sites which are selectively subjected to the greatest impact of, and contact with, the blood stream, and, thereby, with the bacteria and bacterial products circulating within that blood stream. Accordingly, stenotic and insufficient valves, particularly at their distal edges, are common sites of localization. On the basis of this concept, the attempt was made to account for the fact that vegetations are found with great frequency (1) on rheumatic, fibroplastically deformed valves, (2) on the left side of the heart, and (3) at sites of congenital malformations. It was pointed out further that the organisms which cause acute bacterial endocarditis manifest a greater predilection for the right side of the heart than do those responsible for subacute bacterial endocarditis. This fact dovetails with the concept on the theoretical ground that the virulent organisms which give rise to acute endocarditis, e.g., the *Streptococcus hemolyticus*, gonococci, etc., require the advantages of "impact and contact" to a lesser extent because of that virulence. These conceptions are obviously directly opposed to the theories that the localization of vegetations is determined by bacterial embolism through the medium of the coronary arteries, by impingement of the cusps against each other at the line of closure, or by eddy currents.

At the time of the original communication it was realized that many odd sites of localization of vegetations are encountered, principally because of cardiac anomalies, but also as a result of distortions caused usually by previous rheumatic involvement or, rarely, by foci of healed myomalacia (e.g., with perforation of the interventricular septum). To render a theory of localization tenable, it is obviously mandatory that the same general principles be applicable to each case, notwithstanding marked differences in the underlying physical conditions. The following case illustrates this point.

#### CASE REPORT

*History.*—S. S. (445775). The patient was a 15-year-old white schoolgirl with a history of "heart disease," diagnosed at the age of 7 years. There had been

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From the laboratories of The Mount Sinai Hospital.  
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\*George Blumenthal, Jr., Fellow in Pathology.

no restriction of activity, however. Three weeks before admission she experienced chills, fever, marked weakness, and slight cough with bloodtinged sputum. A week later a course of sulfapyridine was started, but it was discontinued because of hematuria.

*Physical Examination.*—The temperature was 102.4° F.; the pulse rate, 86; and the respiratory rate, 20. The patient was well developed, pale, and slightly dyspneic. There were several petechiae on the soft palate. There was no clubbing of the fingers or toes. The arteries of the neck pulsated prominently, and the cervical veins were distended. The heart was enlarged both to the right and left. The apical impulse was diffusely palpable in the region of the sixth left intercostal space in the anterior axillary line. There was a coarse systolic and diastolic thrill, most pronounced in the second interspace near the sternum, which was transmitted to the left and downward, as well as upward for a slight distance. There was a loud, roaring, to-and-fro, almost continuous murmur, with a systolic accentuation, in the same areas. The heart sounds were completely obscured by this murmur except at the apex, where the second sound was loud and snapping. There was some question of an independent diastolic component at the aortic area to the left of the sternum. The pulse was of the Corrigan type, with a loud pistol shot and a Duroziez sign. The blood pressure was 130/20. There was a marked capillary pulsation. The tip of the spleen was felt about 2 cm. below the costal margin. The liver was not palpable.

*Laboratory Data.*—The hemoglobin was 73 per cent; the erythrocyte count, 3,730,000; and the leucocyte count, 6,800; the differential count was normal. The urine contained albumin (+++) and a few erythrocytes and leucocytes. The blood Wassermann reaction was negative. The blood urea nitrogen was 12 mg. per cent. Blood culture revealed sixty colonies of *Streptococcus viridans* per cubic centimeter. A roentgenogram of the chest showed a marked widening of the contour of the heart which was suggestive of pericardial effusion. The electrocardiogram revealed sinus tachycardia; the P-R interval was 0.2 second; the QRS wave was slightly slurred and measured 0.1 second. The electrocardiogram was interpreted as indicating myocardial disease. A phonocardiogram demonstrated a high-pitched murmur which was present throughout systole and continued, at least in certain areas, into diastole. Also, a diastolic, high-pitched murmur was recorded over the mesocardium and the pulmonic area.

*Course.*—The patient received 1 Gm. of sulfanilamide every four hours for seven days (total dose, 41 Gm.). Nevertheless, she continued to have a fever which ranged from about 100° to 104° F. Eleven days after admission the patient was transfused, and she died several hours later.

*Clinical Diagnosis.*—The possibilities considered were patency of the ductus arteriosus with patency of the interventricular septum, or an aortic lesion, or both, and subacute bacterial endocarditis.

*Autopsy.*—The autopsy was performed four hours after death. The body was that of a well-developed, but poorly nourished, 15-year-old white girl, with marked pallor of the skin and mucous membranes. There was no clubbing of the fingers or toes. There was a bilateral pleural effusion (750 c.c. on the right and about 500 c.c. on the left). The spleen was enlarged; it extended 5 cm. below the costal margin in the left anterior axillary line.

*Heart.*—The heart was distinctly enlarged and weighed 575 Gm. There were about 40 c.c. of clear, light-yellow fluid within the pericardial sac. The epicardial surface was smooth and glistening except for several small, gray-white, firm flecks on the posterior aspect of the right auricle. This chamber was not dilated or hypertrophied. The foramen ovale was closed. The opening of the coronary sinus was in its normal position. The ring of the tricuspid valve measured 11 cm. in circumference. The cusps were not thickened, and the chordae tendineae were thin and inserted in a weblike manner. The right ventricle was moderately dilated and

hypertrophied. The wall measured 6 mm. in thickness at a distance of 2.5 cm. from its base. The ring of the pulmonic valve measured 76 mm. in circumference. The cusps were slightly thickened at their distal edge, but were pliable, and there was no stenosis. At the bases of the cusps there were clusters of finely granular, friable, tawny vegetations which averaged 1 to 2 mm. in height. Directly below the anteroposterior commissure there was an oval, obliquely placed interventricular septal defect which measured 1.5 by 1.2 cm. Protruding through this defect, and occluding about nine-tenths of it, was the folded right cusp of the aortic valve



Fig. 1.—A, Left ventricle. Note regurgitation pockets, with small vegetations on superior aspect. Note also vegetations at base of posterior aortic cusp. B, Right ventricle. Observe the interventricular septal defect, with eventrated right aortic cusp anchored to anterior pulmonic cusp. The vegetations partially rim the defect and involve the aortic and bases of the pulmonic cusps. The free edges of the cusps are spared, as is the mural endocardium opposite the septal defect. Note the "stenotic" endocardial pockets (arrow).

(Fig. 1). This position of the aortic cusp must have been constant, because it was firmly anchored near its base by fusion with the anterior pulmonic cusp. The septal defect was rimmed over approximately two-thirds of its circumference by finely granular, small vegetations which were also present on the lateral aspect of that portion of the aortic cusp which protruded into the right ventricle. A Gram stain of the crushings of these vegetations revealed numerous Gram-positive cocci in pairs



and short chains. *Streptococcus viridans* was obtained from a culture of the vegetations. Smoother, dew-drop vegetations, 1 to 2 mm. in height, were located in the mural endocardium directly along the outflow tract of the right ventricle. The subvalvular endocardium was thickened and gray-white. There were, in addition, endocardial pockets which faced in a direction opposite that of the pulmonic valve (Fig. 1B). There were no vegetations in these pockets.

The left auricle was slightly dilated and hypertrophied. There was moderate wrinkling and thickening of the endocardium of the posterior wall of the auricle. The ring of the mitral valve measured 10 cm. in circumference. There was minimal thickening of the free edge of the valve at the junction of the anterior and posterior cusps. However, the chordae tendineae were thin and were inserted into the substance of the valve in the normal fanlike fashion. The left ventricle was distinctly dilated and hypertrophied. Its cavity measured 11 by 12.5 cm., and its wall was 24 mm. thick at a distance of 4.5 cm. from the base. The papillary muscles were hypertrophied. The myocardium was of a homogeneous, purple-brown color, except in the subendocardial zones of the papillary muscles, where it was yellowish tan. The aortic ring measured 65 mm. in circumference. The posterior cusp was large; it measured fully 24 mm. in breadth. Its free edge was rolled, but its commissures were not fused. There was a slight, glistening nodularity of the ventricular aspect of the cusp. In the right lateral portion of the base of the cusp there was an irregular 3 by 3 mm. vegetation. The right and left cusps were fused, although a distinct raphe persisted between them. Almost the entire right aortic cusp, which was diffusely thickened to a slight degree, was folded into the interventricular defect in such a way that the resistance offered by this cusp to the column of blood returning in diastole must have been negligible. In consequence, there was a distinct aortic insufficiency. The point of major interest lay in the endocardial ridges and regurgitation pockets, which were approximately 22 mm. and 26 mm. below the level of the free edge of the aortic valve (Fig. 1d). They were at the site where the blood returning in diastole through the insufficient valve would impinge on the mural endocardium. The small insufficiency pockets faced, in characteristic fashion, in the same direction as the normal aortic cusps, and in a direction opposite that of the endocardial pockets caused by stenosis, such as those which were found in the right ventricle (Fig. 1). These pseudo valves were covered at their free edges and in their depths with fine, granular, tawny vegetations. Other small regurgitation pockets were present near the posterior papillary muscles. These, too, lay in the path of the diastolic backflow. One of the endocardial ridges referred to above was slightly undermined in a direction facing the apex of the heart. There were no vegetations at either of these sites.

The coronary ostia were widely patent, and the vessels showed a minimal degree of sclerotic narrowing.

There were no pertinent changes in the remaining organs. Permission to examine the brain was not obtained.

*Microscopic Observations.*—Sections through the insufficiency pockets revealed the presence of the characteristic vegetations of bacterial endocarditis, superimposed on a fibrous projection of mural endocardium. The bulk of the reaction was localized to the superior, free edge of the pockets. The bases of these vegetations were composed of a vascular, apparently recently formed, cellular granulation tissue, in which the principal cell was a large, vesicular histiocyte. These histiocytes exhibited a slight tendency toward vertical arrangement and palisading. Van Gieson's stain and Mallory's aniline blue stain showed that the fibrous tissue of the underlying regurgitation pockets frayed out and merged with the granular, fibrinoid material which composed the periphery of the lesion. In some portions of the periphery the collagenous fibers were disrupted into small, granular fragments which extended to the very edge of the vegetation. One frequently saw nonnucleated fibers of col-

lagenous tissue fanning out from the fibrous pseudo valve toward the fibrinoid periphery. These fibers manifested a progressive loss of affinity for the acid fuchsin of the van Gieson stain until, near the edge of the lesions, they stained yellow and resembled strands of fibrin (Figs. 2 and 3).



Fig. 2.—Contrast sections of regurgitation pocket stained with H & E (A) and Weigert's elastic tissue and van Gieson's stain (B). Note that the vegetation, which closely resembles a simple thrombotic deposit in A, is found really to contain isolated fragments of disrupted, nonregenerative, collagenous tissue (D). Note the frayed collagenous fibers at the base of, and within, the vegetation (2).

A section through the anterior cusp of the pulmonic valve revealed evidence, in the form of proliferation, palisading and vertical arrangement of basophilic histiocytes, hypercapillarization, and eosinophilic degeneration of the elastic and collagenous tissue, of acute rheumatic inflammation. The cellular infiltration was found on both the ventricular and arterial aspects of the valve. At its base there was a vegetation characteristic of bacterial endocarditis. More distally, along the ventricularis, there were minimal, superficial foci of bacterial endocarditis. A section through the vegetations on the posterior aortic cusp presented a similar picture of acute rheumatic endocarditis, combined with bacterial inflammation.

Sections of the myocardium revealed scattered Aschoff bodies. There was also slight myofibrosis, which was principally perivascular in distribution.

The histologic changes in the remaining organs were not significant; the focal renal glomerular lesions which are characteristic of subacute bacterial endocarditis were absent.



Fig. 3.—High-power magnification of portion of Fig. 2B. Note the collagenous fibers (arrows) merging with the fibrinoid, necrotic tissue. If these few remaining fibers had been destroyed, as not infrequently happens, the vegetations would be almost indistinguishable from a simple thrombotic deposit.

#### *Anatomic Diagnoses.—*

1. Congenital heart disease
  - a. Patency of membranous portion of interventricular septum.
  - b. Eventration of right aortic cusp into septal defect and fusion of it with anterior pulmonic cusp.
  - c. Aortic insufficiency and pulmonic stenosis.
  - d. Moderate dilatation and hypertrophy of both ventricles.
2. Rheumatic heart disease
  - a. Acute rheumatic aortic and pulmonic valvulitis.
  - b. Acute rheumatic myocarditis.
3. Bacterial endocarditis (*Streptococcus viridans*) involving:
  - a. Margin of ostium of septal defect in right ventricle.
  - b. Mural endocardium of right ventricle.
  - c. Endocardial regurgitation pockets in left ventricle.
  - d. Posterior and right aortic cusps.
  - e. Pulmonic valve.
4. Pulmonary edema and congestion.
5. Bilateral hydrothorax.

#### DISCUSSION

The physical conditions in this case were as follows: The base of the right aortic cusp was firmly adherent to the anterior pulmonic cusp. This anchorage, which was apparently congenital, was made possible by the patency of the membranous portion of the interventricular septum. As a result, most of this aortic cusp lay within the septal defect and practically occluded it, although there appeared to be sufficient residual patency to account in part for the systolic thrill and murmur.

In addition, a portion of this same cusp actually projected into the right ventricle, with the result that a stenosis was produced. This stenosis was more likely the major cause of the systolic thrill and murmur. There was striking indirect evidence of the existence of a stenosis, namely, the presence of subvalvular endocardial pockets which faced in a direction opposite that of the pulmonic valve, and a diffuse, subvalvular, endocardial sclerosis (Fig. 1B). Inasmuch as the pulmonic cusps could not have produced the stenosis, the protruding, fixed aortic cusp must have been responsible for it. In other words, the level of the narrowed orifice was not at the free edge of the valve, as it is in ordinary cases of rheumatic pulmonic stenosis, but rather at the site of protrusion of the eventrated aortic cusp and at the bases of the pulmonic cusps, which were approximately on the same plane. Furthermore—and this is the point to be emphasized—the vegetations were located, not at the line of closure of the valve, where they are ordinarily situated, but at the level of the stenosis. In this case, the level of stenosis was below the distal edge of the cusps because an anomalous, protruding aortic cusp encroached on the pulmonary outlet. *This is the site which suffered the greatest impact of, and contact with, the blood stream* because of the accelerated velocity of ejection, frictional resistance, and exposure to a greater surface area of blood, and, therefore, to a greater number of bacteria, as well as to other hemodynamic factors which are discussed in more detail elsewhere.<sup>1</sup>

The presence of a minute, superficial lesion of bacterial endocarditis near the mid-portion of the ventricular aspect of the pulmonic and aortic cusps, and the characteristic absence of involvement of the arterial surface are regarded as direct consequences of the fact that a greater quantity of blood, and of bacteria, brushed by the ventricularis than by the opposite surface during each cardiac cycle. This selective localization occurred in spite of the acute rheumatic involvement of both aspects of the cusps. Stated in another way, the entire ventricular surface of the semilunar valves suffered the hemodynamic disadvantage of selective "contact," which, in this case, was enhanced at the base of the pulmonic valve by the presence of stenosis at this level.

Small mural vegetations were also found directly along the outflow tract of the right ventricle, where the effects of the stenosis were, of course, felt, albeit to a lesser degree.

The left ventricle presented an even more striking demonstration of the dominant role which the factors of impact and contact play in the selective localization of vegetations. Because of the eventration of the right aortic cusp, there was a marked incompetence of the aortic valve; this was localized to the site normally occupied by this cusp. This leak was apparently the cause of the diastolic murmur. Immediately below this site there was striking evidence, in the form of endocardial pockets which faced in the same direction as normal aortic valves (Fig. 1A), of

the insufficiency. Shallow endocardial pockets or curved endocardial ridges are sometimes referred to as Zahn's<sup>3</sup> valves, and the larger, deeper, horseshoe-shaped pockets as Sehmler's<sup>4</sup> valves. It is relevant to mention briefly the theories of the pathogenesis of these endocardial pockets. These include the (1) mechanical (constant impingement of a regurgitant stream of blood), (2) congenital, and (3) inflammatory (Ribbert<sup>5</sup>). It is important to be reasonably certain that the formation of the endocardial pockets in this case preceded the bacterial endocarditis. However, the bacterial endocarditis could hardly have led to the formation of these pseudo valves, for parts of the immediately adjacent endocardial ridges and pockets were composed of old fibrous tissue which was entirely free of endocarditis. Exclusion of the possibility that the pockets were congenital is made difficult by the fact that there were coexistent cardiac anomalies. However, in the presence of frank aortic insufficiency, these pockets were more likely caused by the continual impact of the regurgitant stream against the mural endocardium.

It is clear, then, that these endocardial outpouchings suffer, to a selectively increased degree, the brunt of impact by the diastolic stream as it returns through the insufficient valve and is reflected from this part of the wall. This repeated pounding leads to local fibrous tissue thickening of the endocardium, and this is molded by the jet into a shallow pocket. It was, therefore, not surprising, but rather in conformity with the principles of the concept, to find vegetations localized to these endocardial pockets to the exclusion of other portions of the mural endocardium of this chamber. Still more graphic confirmation was afforded by the histologic observation that the vegetation was practically confined to the depth and free edge of the pocket, where the direct impact of, and contact with, the diastolic backflow would be greatest, whereas the more protected undersurface was essentially spared (Fig. 2). It is interesting, also, that the vegetation was located at the base of the posterior aortic cusp, in direct line with the diastolic stream.

*Nature of the Vegetations.*—Another point of major interest lies in the nature of these vegetations. The histologic evidence bears out the conclusion reached elsewhere (Allen<sup>2</sup>) that the vegetations of bacterial endocarditis are not thrombi deposited from the blood on an inflamed endocardial surface, but are really derived from necrotic valvular tissue, forced apart by the plasma and blood elements which are exuded from the eroded or abnormally permeable valvular blood vessels that are part and parcel of inflamed valves. In this connection, one is reminded of the remarkable frequency with which atheromatous "ulcers," with no overlying endothelium, occur in the aorta without superimposed thrombi. It is, of course, maintained that the bacteria are implanted upon the valves from the blood within the chambers in the vast majority of instances.

## SUMMARY AND CONCLUSIONS

1. A case of bacterial endocarditis caused by *Streptococcus viridans*, in a heart with a large interventricular defect through which an aortic cusp had eventrated, with resulting pulmonic stenosis and aortic insufficiency, is reported.

2. The vegetations were localized to regurgitation pockets in the mural endocardium of the left ventricle, where there was constant impact by the regurgitant stream as a result of the aortic insufficiency.

3. The localization of vegetations at sites which are subjected to various hemodynamic forces is explained as the result of impact of, and contact with, the blood stream, and with bacteria circulating therein.

4. The histologic observations confirmed the concept previously advanced, namely that the vegetations of bacterial endocarditis are derived from necrotic valvular tissue, and the plasma and blood elements from eroded valvular blood vessels; this occurs after implantation of bacteria from blood within the chamber. This is contrary to the current concept that the vegetations are thrombi which are deposited on an inflamed endocardial surface as the blood flows past the valves.

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# Department of Reviews and Abstracts

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## Selected Abstracts

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Asmussen, Erling, and Chiodi, Hugo: The Effect of Hypoxemia on Ventilation and Circulation in Man. *Am. J. Physiol.* 132: 426, 1941.

*Respiration.*—Experiments have shown that hypoxemia caused by partial CO poisoning (20 to 30 per cent) (anemic hypoxemia) elicits little or no respiratory response whereas hypoxemia caused by an alveolar  $pO_2$  of about 40 mm. Hg (hypoxic hypoxemia) causes a very pronounced hyperventilation in both rest and work.

It is concluded: 1. General  $O_2$  deficiency in the tissues does not evoke a hyperventilation. 2. The  $O_2$  tension of the arterial blood, and not its  $O_2$  content, is the active factor in causing hyperventilation. 3. The effect is produced through the  $pO_2$  of the carotid body (glomus).

*Circulation.*—Experiments have shown that both in rest and during work a state of hypoxic hypoxemia, with the  $O_2$  in the inspired air low enough to reduce the arterial  $HbO_2$  to 70 or 80 per cent, produces an increase in cardiac output above the normal. Furthermore, both in rest and during work a state of anemic hypoxemia (20 to 30 per cent Hb saturated with CO) has little or no effect on cardiac output, but increases the pulse rate considerably.

It is concluded: 1. Acute  $O_2$  deficiency in the tissues is not a stimulus for the circulation. 2. A lowered  $O_2$  tension of the arterial blood, not a lowered  $O_2$  content, is a stimulus for the circulation. 3. The effect probably is produced through the chemoreceptors of the carotid glomus.

AUTHORS.

Mangun, George H., Reichle, Herbert S., and Myers, Victor C.: Further Studies on Human Cardiac and Voluntary Muscle. Possible Implications of Changes in the Creatine, Phosphorus, and Potassium Content, With Special Reference to Heart Disease. *Arch. Int. Med.* 67: 320, 1941.

Creatine, phosphorus, and potassium determinations have been carried out on samples of muscle from the left and right ventricles of hearts obtained at autopsy from human beings with pathologic conditions. In forty-eight instances analyses were also carried out on voluntary muscle.

The content of creatine, phosphorus, and potassium in the left and right ventricles and in voluntary muscle averaged about 5 per cent less than in samples from thirteen normal persons and varied considerably more.

In seventeen patients with congestive heart failure, the creatine, phosphorus, and potassium concentrations of both ventricles and of voluntary muscle were consistently decreased. The percentage decrease was greatest for creatine and least for phosphorus, while potassium occupied an intermediate position.

The average figures obtained for persons with heart failure showed a loss of 4.0 mols of creatine, 6.0 mols of phosphorus, and 9.4 mols of potassium per kilogram. It is suggested that this loss is due primarily to a breakdown of dipotassium phosphocreatine with a subsequent loss of its components.

In uremia the creatine, phosphorus, and potassium contents of voluntary muscle were found to be somewhere higher than the average values, 50 per cent of the

values being higher than the normal range. Values for cardiac muscle were also relatively high. The increase in the creatine content of voluntary and cardiac muscle in uremia finds probable explanation in the retention of creatinine and the equilibrium which exists between creatinine and creatine. The changes in the phosphorus and potassium are probably related to the creatine changes.

The creatine, phosphorus, and potassium values tended to be decreased in voluntary muscle in all conditions not associated with nitrogen retention, with the possible exception of fever and emaciation. Values in cardiac muscle, on the contrary, were usually normal or slightly elevated, unless heart disease was evident.

AUTHORS.

Landt, Harry, and Benjamin, Julien E.: Changes in the Content of Carbon Dioxide in Venous Blood During Rebreathing Experiments. Comparison of Change in Persons With a Normal Heart and in Patients With Cardiac Disease. *Arch. Int. Med.* 67: 72, 1941.

When subjected to rebreathing experiments, patients with cardiac disease lose carbon dioxide from the blood stream. Normal persons either maintain the carbon dioxide content or gain when subjected to like conditions. The loss of carbon dioxide from the blood stream of the patient with cardiac disease allows for a relatively greater oxygen-carrying power in the blood.

AUTHORS.

Sussman, Ralph M., and Lieberman, Abraham: Chest Lead Changes as the Sole Electrocardiographic Evidence of Heart Disease. *Brit. Heart J.* 3: 13, 1941.

Four thousand four-lead electrocardiograms (3,200 cases) were reviewed to assess the diagnostic value of an abnormal precordial lead when the standard leads were normal. The criteria adhered to as a basis for this selection were an absent R wave, an R wave of less than 2 mm., a QRS wave of M or W configuration, or an inverted T wave, these being found in the fourth lead, in the presence of standard leads that were without significant alterations. Of the 3,200 cases, seventy showed positive precordial and negative standard leads. Of these seventy, a characteristic group of twenty-three was completely analyzed as representative of the larger group. By careful history, physical examination, and x-ray the twenty-three cases with positive chest leads were divided into a cardiac group (57 per cent) and a noncardiac group (43 per cent). Left axis deviation occurred with about equal frequency in both groups. Coronary thrombosis was present in only one patient (8 per cent) of the cardiac group. Pulmonary disease contributed the great number of cases to the noncardiac group (four of ten). Absence of the initial upward deflection (R wave) in Lead IV was the most common finding in the cardiac group (five of thirteen cases). Low R waves occurred with about equal frequency in both groups. Inverted or biphasic T waves were present slightly more often in the noncardiac than in the cardiac group. The female sex was predominant in the ratio of about 3 to 1 in both groups.

Where the standard leads were normal, the precordial lead was the sole electrocardiographic indicator of heart disease in 1 to 2 per cent of 3,200 cases studied. An abnormal fourth lead in the presence of normal standard leads is indicative of heart disease in more than 50 per cent of such cases.

An absent R wave is of greater significance as a sign of myocardial damage than are either low R waves or inverted T waves, alone or combined.

The precordial lead may be the only electrocardiographic evidence of heart disease in conditions other than coronary thrombosis or sclerosis.

AUTHORS.



Schnur, Sidney: T-Wave Inversion, Heart Size, and Functional Capacity. *Brit. Heart J.* 3: 30, 1941.

The electrocardiogram, functional capacity, and cardiac size were correlated in a study of 100 consecutive patients with hypertension. There is a positive correlation between the size of the heart and functional capacity.

As the heart enlarges in hypertension, the T wave progressively becomes inverted in Leads I and II and upright in Lead III. The RS-T segment follows the T wave in its direction.

Left ventricular preponderance is a characteristic electrocardiographic pattern occurring in 35 per cent of patients with enlarged left ventricles. It occurs with increasing frequency as the heart enlarges and is characterized by (1) left axis deviation, (2) inversion of  $T_1$  or of  $T_1$  and  $T_2$  with  $T_3$  upright, and (3) a depressed RS-T segment in Lead I or in Leads I and II and an elevated RS-T segment in Lead III.

Since functional capacity and cardiac size are both directly related to left ventricular preponderance, one may estimate, with some degree of accuracy in many cases, the functional capacity and approximate size from the electrocardiographic picture.

Because depressed RS-T segments in Leads I and II and elevated RS-T in Lead III are found in 35 per cent of enlarged hypertensive hearts, and this deviation is one of the cardinal patterns of posterior coronary occlusion, one should be extremely careful in making the latter diagnosis on the cardiographic evidence alone. The origin of the RS-T take-off and the presence of Q waves are of value in the differential diagnosis.

Hypertension is the most frequent etiological cause of left ventricular preponderance. Syphilis is the next most common etiological factor.

There is no positive correlation between the level of the blood pressure and these changes. The data do not solve the problem of whether the duration of hypertension, enlargement, per se, or some other factor associated with enlargement is responsible for the T and RS-T changes.

It is not believed that the few cases of coronary occlusion or overdigitalization in the series affect the general conclusions.

AUTHOR.

Eliaser, Maurice, Jr., and Kondo, Benjamin O.: The Electrocardiogram in Later Life. *Arch. Int. Med.* 67: 637, 1941.

A group of 100 active, employable, asymptomatic persons between the ages of 70 and 92 years, who presented no clinical evidence of cardiac disease other than systolic mitral murmurs of the arteriosclerotic type and slow, untreated auricular fibrillation, were examined electrocardiographically.

Certain electrocardiograms which are usually considered pathologic occurred with sufficient frequency to be considered normal for this age group. They included records of left axis deviation, abnormally low voltage, sinus bradycardia, partial latent auriculoventricular conduction defects, intraventricular conduction defects, and inversion and flattening of the T waves in any or all leads.

Some changes occurred in a sufficiently small percentage of persons to warrant the impression that, when noted, they could be considered only presumptive evidence of myocardial disease. These were auricular fibrillation, bundle branch block, elevation of the ST intervals above the base line, especially in the first standard lead, and the occurrence of the type of QT changes in Lead I associated with anterior coronary occlusion.

Definite abnormalities of the cardiovascular system were suggested by electrocardiographic changes in which a prominent Q wave was observed in association with an inversion of the T wave in Lead IV F, complete auriculoventricular dissociation, and right axis deviation.

It is intimated that greater care must be taken in the interpretation of the electrocardiograms of persons in later life than in the interpretation of those of the younger age groups if errors of commission are to be avoided in the diagnosis of acute lesions of the coronary arteries.

AUTHORS.

Hamilton, F. Carlyle: *The Significance of Gallop Rhythm.* Canad. M. A. J. 44: 260, 1941.

Gallop rhythm is a fairly common and easily recognizable sign of serious heart disease. It must not be confused with the rhythm created by a third physiologic heart sound.

Gallop rhythm occurs chiefly in connection with long-standing hypertension. It is always associated with serious heart disease.

The three types of diastolic gallop occur with equal frequency. The protodiastolic type has the most serious outlook.

Some evidence is presented to suggest that the prognosis is most serious when gallop rhythm occurs during the fourth decade of life, since many of these cases result from hypertension secondary to chronic nephritis or from malignant hypertension.

In older patients with gallop rhythm the immediate prognosis was found to be somewhat better than anticipated; this should encourage us to treat thoroughly the underlying heart condition in all such cases.

AUTHOR.

Scherf, David: *An Experimental Study of Reciprocating Rhythm.* Arch. Int. Med. 67: 372, 1941.

An auriculoventricular rhythm was produced in dogs' hearts in situ; functional longitudinal dissociation appeared after the conduction system was fatigued by means of a series of extrasystoles or during stimulation of a vagus nerve. In this stage return extrasystoles (reciprocating beats) appeared whenever the R-P interval of the auriculoventricular beats was prolonged. The experiments prove that under certain conditions bigeminal or trigeminal rhythm may be due to a re-entry mechanism.

AUTHOR.

Stewart, Harold J., and Bailey, Robert L., Jr.: *The Cardiac Output and Other Measurements of the Circulation in Coarctation of the Aorta.* J. Clin. Investigation 20: 145, 1941.

This study concerns fourteen cases of coarctation of the aorta. The diagnosis was made during life in thirteen of these and at autopsy in one case; in four cases it was confirmed by autopsy in patients who died some time after the diagnosis had been made.

The following observations were made in nine of these cases: cardiac output, basal metabolic rate, arteriovenous oxygen difference, cardiac output per beat, left ventricular work per beat, the blood pressure in all four extremities, venous pressure, vital capacity, circulation time by means of decholin, carbon dioxide inhalation,

and maseosol, electrocardiograms, and x-rays of the chest. Clinical observations of five other patients are included in Table I.

The heart at rest was found to maintain a normal or even increased volume output of blood in coarctation of the aorta before the onset of failure. In only one of the nine cases was the cardiac output decreased. In only one of these patients was the heart enlarged to give a cardiothoracic ration greater than 50 per cent. The work of the heart in relation to the cardiac size was, as a consequence, adequate in all except this one case. This patient had a cardiac output within normal limits, but it was not in proportion to the greatly enlarged heart.

The systolic blood pressure in the arms was higher than that in the legs in all except one patient. This finding was the most constant of the characteristic signs of coarctation of the aorta. In most cases, there was not only an increase in the resistance to the outflow of blood at the site of coarctation and in the collateral channels, but also a generalized increase in peripheral resistance sufficient to maintain a high diastolic pressure below the level of the coarctation.

The circulation time was within or near normal limits above the level of coarctation, but there was a tendency to prolongation below the coarctation.

Erosion of the inferior margins of the ribs posteriorly, giving rise to scalloping and notching, was the most common x-ray finding in coarctation of the aorta. This was noted in eleven of the fourteen cases.

Enlargement of the heart and T-wave changes in the electrocardiogram point to poor prognosis when they occur.

AUTHORS.

Bedford, E. Evan, Papp, Cornelio, and Parkinson, John: Atrial Septal Defect. *Brit. Heart J.* 3: 37, 1941.

A patent foramen ovale (patent to probe or even to pencil), found in 20 to 30 per cent of all necropsies, is an anatomic variation of a normal condition; it is clinically silent except that, when it is distended by increased right auricular pressure ("widely patent"), it can give rise to terminal cyanosis and paradoxical embolism. In contrast, atrial septal defect (A.S.D.) is a real congenital malformation due to a defective union or malformation of the three embryonic septa forming the definitive atrial septum. It occurs (a) as a single lesion and constitutes 7 to 25 per cent of all congenital heart lesions, (b) as an associated lesion with any other congenital heart lesion, and (c) combined with mitral stenosis, and then probably with auricular fibrillation.

A diagnosis of A.S.D. was made in fifty-three patients, ten with necropsy control and forty-three without. An association with mitral stenosis was present in four of the necropsy cases (one also had adhesive pericarditis), in four of the clinical cases, and with patent ductus arteriosus and ventricular septum defect in one necropsy case. The lesion may be found at any age, and the prevalence of females was striking (4:1). The age of death was mostly between 20 and 50. The cause of death was congestive heart failure in three, pulmonary infarction in two, embolism (one paradoxical) in two, subacute bacterial endocarditis in one, bronchopneumonia in one, and operation in one.

The pathologic findings in the ten necropsy cases were:

(a) A large heart consisting mainly of right ventricle, conus, and right auricle, with a disproportion between right and left cavities of about 3:1 in bulk, or even more in cases of associated mitral stenosis.

(b) Gross dilatation of the pulmonary artery and its branches, except in one case where there was a big conus with a normal pulmonary artery. Severe arteriosclerosis (with thrombosis of the pulmonary artery and branches) was found only once, and in lesser degree three times; the remainder showed simple thickening only.

(c) The atrial septum was almost absent in one; the defect involved the lower part of the septum, and there was an imperfect formation of the tricuspid valve (persistent ostium primum) in another; and its site was the enlarged fossa ovalis or the upper part of the septum in the remainder. The dimension of the defect varied from 1 by 0.8 cm. to 7 by 4 cm. There was no strict relation between the dimension of the defect and the degree of pathologic adjustment.

Auditory signs in A.S.D. are lacking, for the lesion itself produces no murmur. Any murmurs heard are due to dilatation of the right ventricle and the conus, and relative stenosis of the less distensible pulmonary ring. A systolic murmur in the pulmonary area was found in thirty-two and was accompanied by a systolic thrill in thirteen cases. An accentuated pulmonary second sound in thirty-one was followed by a diastolic murmur in ten; no murmurs were recorded in eight cases. A forcible and displaced apex beat without other cause and due to the large right ventricle proved to be a most suggestive sign (thirty-two cases). Common clinical features in our fifty-three cases were fair capacity for exertion even with an enlarged heart and signs of failure (twenty-seven cases) and slight cyanosis on effort or late cyanosis (thirty-one cases). Underdevelopment, though occasionally seen (eight cases), was far less frequent than in other published statistics.

The radiological features in fifty-one cases indicated their paramount importance in diagnosis. General enlargement was present in forty, chiefly to the left in thirty. The prominence of the left border proved to be due, however, to the enlarged right ventricle which displaced the left ventricle backward. Great projection of the right auricle points to coexisting mitral stenosis. The bulging of the pulmonary stem and conus with the enlarged, dense, right hilum shadow (right branch of the pulmonary artery) gives the heart its striking appearance in the anterior view. Excessive pulsation of the hilum was noticed in thirty-one instances; but a real "hilar dance" could be seen in only five, and then there was not always pulmonary incompetence. Lack of pulsation with increased density was diagnostic of local thrombosis in one necropsy case. The aorta was small or invisible in about half of the cases. In the right (I) oblique view the enlargement of the pulmonary stem and conus became even more evident, and a pulmonary impression on the esophagus was observed in eighteen of our cases. In the left (II) oblique view, the enlarged left pulmonary branch obscured the aortic window, and the right ventricle was unduly convex. Negative radiological signs of importance were the absence of the left auricular curve in the right oblique view and the absence of lung congestion. In the six cases where the left auricular curve was prominent it was proportionate to the general cardiac enlargement. Pulmonary congestion was found in only three cases having severe failure, and hydrothorax in only two—both in terminal conditions.

The electrocardiogram often helped in diagnosis. Normal rhythm was the rule (in forty-seven), and, when auricular fibrillation was present, it was not due to the lesion itself but either to rheumatism (mitral stenosis) or to age changes. Right axis deviation was very frequent (in forty-one), if we include partial right bundle branch block (26); complete right bundle branch block of the older or newer type was found in five.  $T_2$  and  $T_3$  were inverted independently of the bundle branch block character of the ventricular complex (in nine). A prolonged P-R interval of 0.20 second or over, and large or bifid P waves were not infrequent.

Failure appeared usually between the ages of 30 and 50 and was typically right ventricular. Late cyanosis and liver enlargement were its main features; dyspnea was moderate, and pulmonary congestion was rare except in the terminal stage when edema and ascites might supervene. Pulmonary infarction early in the course was rare and then based upon pulmonary arteriosclerosis. Subacute bacterial endocarditis as a complication was exceptional (one necropsy case). The mechanism of

failure is explained by the increased blood volume that the right ventricle has to propel, for the left atrium with its higher pressure partly diverts through the defect blood from the left cavities. We cannot accept the hypothesis recently advanced by French authors that the disproportion between right and left cavities and between pulmonary artery and aorta, respectively, is due to a congenital malformation unless A.S.D. is associated with or without mitral stenosis. The similarity of the pathologic findings in A.S.D. with or without mitral stenosis, the progressive dilatation of the right ventricle, and the often normal aorta make us reject this view.

Differential diagnosis is concerned with all congenital or acquired heart conditions in which there is a dilatation of the pulmonary artery and its branches, and these are enumerated. Pulmonary artery disease and primary dilatation of the pulmonary artery with right ventricular hypertrophy, so-called pulmonary hypertension, can produce a similar radiologic and pathologic picture. But these are exceptional conditions, while atrial septal defect is a far more likely cause of gross dilatation of the pulmonary artery and its branches.

AUTHORS.

Lowry, Frederick C., and Burn, Caspar G.: Spontaneous Rupture of the Posterior Papillary Muscle of the Heart. *Arch. Path.* 31: 382, 1941.

This is a report of another case of rupture of the papillary muscle following infarction of the posterior myocardial wall. It is believed that the rupture of the necrotic papillary muscle was the result of excessive strain caused by the hypertrophied myocardium and shortened chordae tendineae of the thickened mitral valve.

AUTHORS.

Gross, Paul: Concept of Fetal Endocarditis. A General Review With Report of an Illustrative Case. *Arch. Path.* 31: 163, 1941.

The occurrence of fetal endocarditis has never been established. The macroscopic and microscopic abnormalities considered criteria of fetal endocarditis have been observed also in the presence of congenital cardiac defects which, after study, have been diagnosed as noninflammatory lesions. The assumed etiological pathogen in the reported cases of fetal endocarditis has been either anamnistically absent or variable in identity.

The myocardial lesions usually seen in so-called fetal endocarditis closely resemble healed bland infarcts. Such infarctions may be related to the obliteration of arterio-luminal, arteriosinusoidal and thebesian vessels by the marked parietal endocardial fibrosis.

The valvular and parietal endocardial changes seen in these cases are better explained on the basis of a developmental defect, since they show no inflammatory residua.

The case of a full-term newborn boy is reported. Stenosis of the mitral and aortic valves was present, and the condition resembled strikingly the rheumatic valvular disease of adult life. This condition was associated with hypoplasia of the root of the aorta, rudimentary development of the left ventricular cavity, the presence of a large patent ductus arteriosus, and marked diffuse parietal endocardial sclerosis of the left ventricle. The genesis of these lesions is considered noninflammatory because of the lack of inflammatory residua.

AUTHOR.

Koletsky, Simon: Congenital Bicuspid Pulmonary Valves. *Arch. Path.* 31: 338, 1941.

In 3,600 consecutive autopsies congenital bicuspid pulmonary valve was found in eight (0.22 per cent). Three of these valves occurred in infants and children, and five in adults; five were in males and three in females. In the same group of autopsies were found twenty congenital bicuspid aortic valves, six pulmonary valves, with four cusps, and no aortic valves with four cusps. Two of the bicuspid pulmonary valves were isolated findings, while the remaining ones were associated with other cardiac anomalies. These were the tetralogy of Fallot, bicuspid aortic valve, patent interventricular septum, transposition of the great arterial trunks, cor triatriatum trilobulare, and widely patent foramen ovale.

Morphologically, there were three types of bicuspid pulmonary valve: (1) the simple bicuspid valve; (2) the bicuspid valve in which one of the cusps revealed a congenital ridge in the sinus of Valsalva; (3) the bicuspid valve in which one of the cusps revealed a small fibrous band or frenum in the sinus of Valsalva. The bicuspid pulmonary valve with a congenital ridge is apparently rare.

From the genetic point of view it appears probable that in many instances the formation of the bicuspid pulmonary valve is due to faulty growth or to malposition of the septum which partitions the common arterial trunk into pulmonary artery and aorta.

The bicuspid pulmonary valves in this series were of little if any clinical significance. They were silent, and there was no functional stenosis or insufficiency; the occurrence of such an anomaly was usually incidental to far more serious cardiac deformities. None of the valves showed superimposed inflammation or calcification.

AUTHOR.

Koletsky, Simon: Congenital Bicuspid Aortic Valves. *Arch. Int. Med.* 67: 129, 1941.

In a survey of 3,300 consecutive autopsies, congenital bicuspid aortic valve was found in eighteen cases (0.54 per cent) and was the most common single cardiac anomaly. It occurred in nine infants and children and in nine adults; fourteen of the patients were males and four females, and seven of the adults were more than 35 years old. Next in order of incidence were coarctation of the aorta (sixteen cases) and patent interventricular septum (fourteen cases). The most frequent associated cardiorortic anomalies were coarctation of the aorta, patent interventricular septum, and patent ductus arteriosus, but in nine of the eighteen cases the bicuspid aortic valve was the only congenital deformity in this region. In one instance there was also a bicuspid pulmonary valve.

In seven cases simple bicuspid valves were present, but in eleven instances there was congenital fusion of two cusps, the resultant ridge being at commissure A in six cases, at commissure B in three cases, and at both commissures in two cases; no fusion was found at commissure C. In nine cases the conjoined cusp was larger than the other cusp. The congenital ridge divided the conjoined cusp equally in all but two cases. Retraction of the ventricular aspect of the conjoined cusp opposite the ridge occurred in five cases.

So distinctive as to be practically pathognomonic is the gross character of the ridge, a narrow, hemicylindric, barlike elevation situated at the commissure, directed in the long axis of the aorta, and extending slightly into the sinus of Valsalva, sharply defined, with parallel borders, and devoid of fissures at the proximal portion. The microscopic picture is characteristic. The ridge consists almost entirely of elastica, whorled centrally and continuous laterally with that of the aortic media; the elastica usually overlaps the annulus fibrosus superficially and deeply or only superficially. Blood vessels are scanty, and there is no inflammation.

Koletsky, Simon: Acquired Bicuspid Aortic Valves. *Arch. Int. Med.* 67: 157, 1941.

Eight cases of acquired bicuspid aortic valve were found in a survey of 3,500 consecutive autopsies. Seven patients were males, and one was a female, their ages ranged from 13 to 74 years. In all cases the bicuspid lesion resulted from complete fusion of the left and right coronary cusps, producing a raphe at commissure A (the left coronary—right coronary commissure), while commissures B and C were usually essentially normal. The lesion was uncomplicated in two cases, while in six cases there was superimposed organic disease; namely, four had calcific sclerosis, one had acute rheumatic valvulitis, and one had both calcific sclerosis and endocarditis lenta.

The commissural raphe consisted of a firm ridge of tissue, considerably depressed in the sinus of Valsalva, directed obliquely in the sinus, of greater height and usually of greater width distally than proximally and with a rounded outer surface which occasionally revealed a fissure indicating the line of fusion of the two cusps. Microscopically, the raphe was composed essentially of hyalinized connective tissue, the base of which rested proximally on aortic media and distally on the subvalvular endocardium. Vascularity and inflammation were limited to the distal portion and were usually situated in the lower or the middle third of the ridge, between the ring and the free margin of the cusp.

The fusion of the leaflets was evidently due to inflammation, probably rheumatic in origin. The structure of the raphe corresponded to that of the usual rheumatic commissural lesion, and in seven of the eight cases rheumatic lesions were demonstrated in other parts of the heart. However, the degree of rheumatic involvement was generally slight, being limited essentially or largely to the aortic valve. Patients usually survive such relatively mild rheumatic heart disease and are then predisposed in later life to the development of superimposed calcific sclerosis of the aortic valve.

The commissural raphe of acquired bicuspid aortic valve differs in that it is constituted largely of relatively acellular collagenous tissue, has little or no elasticity, and shows the presence or residua of other disease.

Superimposed disease of the aortic valve was not found in any of the cases in early life, but in the form of rheumatic involvement, endocarditis lenta, or calcific sclerosis it was present in seven of the nine adults. It is only with the greatest rarity that the superimposed disease actually affects the congenital ridge. The study also suggests that this congenital anomaly may predispose to calcific sclerosis.

AUTHOR.

Lisa, James R., Hirschhorn, Louis, and Hart, Crawford A.: Tumors of the Heart  
*Arch. Int. Med.* 67: 91, 1941.

Four cases of metastatic tumors of the heart causing cardiac dysfunction are reported, and the literature is reviewed.

The outstanding feature of cardiac tumors has been the intractable failure without obvious cause. The appearance of cardiac failure or arrhythmia in association with a known malignant growth in some other organ should lead one to consider the possibility of metastasis to the heart. Roentgenologic and electrocardiographic studies are valuable aids.

AUTHORS.

Rytand, David A., and Holman, Emil: Arterial Hypertension and Section of the Splanchnic Nerves. *Arch. Int. Med.* 67: 1, 1941.

Forty patients were observed who underwent section of the splanchnic nerves and removal of three pairs of lower thoracic ganglions, performed in order to relieve

arterial hypertension. The criteria usually given for selection of patients were ignored.

From a consideration of what is known about the pathologic physiology of arterial hypertension and the effects of denervation it would seem that not much could be expected from any such denervating operations.

In general the results were poor. In only one patient was there a brilliant result, although in five others there was some degree of success in reducing blood pressure. Six more patients felt better, but their arterial pressures were not lowered. In nine patients there was no change. Eleven died within a year and a half, with their condition unchanged (transient relief of symptoms occurring in five of these). Eight died within two weeks after the operation.

Such criteria as age, duration of hypertension, vascular complications in the brain and the heart, heart failure, and liability of arterial pressure were not prognostically significant. The main role in deciding the outcome seemed to be played by the presence or absence of malignant hypertension as evidenced by renal and retinal lesions.

AUTHORS.

Stead, Eugene A., Jr., and Ebert, Richard V.: *Postural Hypotension: A Disease of the Sympathetic Nervous System.* *Arch. Int. Med.* 67: 546, 1941.

Patients with postural hypotension do not pool more blood in the lower part of the body on standing than do normal subjects under similar conditions. The pooling of the normal amount of blood causes an abnormal fall in blood pressure. The reflex vasoconstriction, which maintains the arterial pressure in normal subjects under similar conditions, does not occur in patients with postural hypotension and distinguishes it from other types of poor postural adaptation.

Postural hypotension is a disease of the sympathetic nervous system. It cannot be definitely stated whether the involvement of the sympathetic system is peripheral or central. The observations reported in this study point to the interpretation that the lack of vasoconstriction in response to a fall in arterial pressure is produced by a lesion or lesions in the sympathetic centers or their efferent tracts in the central nervous system rather than by lesions in the more peripheral portions of the postural blood pressure reflex arc. In certain patients only the postural vasoconstrictor reflex is affected. If the lesions are more extensive, other signs of loss of sympathetic function may be present, such as disturbances in sweating, absence of vasoconstriction and vasodilatation, in the extremities when the temperature of the body is changed, and absence of an increase in heart rate when the blood pressure is lowered.

AUTHORS.

Eckstein, Richard W., Gregg, Donald E., and Pritchard, Walter H.: *The Magnitude and Time of Development of the Collateral Circulation in Occluded Femoral, Carotid, and Coronary Arteries.* *Am. J. Physiol.* 132: 351, 1941.

The time rate of collateral development has been studied in the femoral, carotid, and coronary arteries by means of the retrograde pressure and flow.

In the femoral artery immediately after occlusion the retrograde pressure and flow approximate 20 mm. Hg and 10 to 15 c.c. per minute, respectively. Immediately a small pulse appears, and these values rise rapidly for a few hours and then more slowly for days and weeks until pulse and flow may approach those existing in the other intact femoral artery.

In the carotid artery the initial retrograde pressure and flow are somewhat greater than in the femoral artery; a pulse is always present, and these approach more quickly the normal for the other carotid.



Following coronary occlusion the retrograde flow is nearly constant at values between 0.5 to 5.8 c.c. per minute, and then after some hours it, together with the peripheral diastolic pressure, increases very slowly to obtain sizable values in a week or so. As in coronary arteries occluded for many weeks, the major source of such retrograde flow may be the other coronary arteries.

Evidence is given to indicate that initial retrograde flow is due to increased differential pressure opening pre-existing collaterals. The mechanism for further collateral extension is not known.

In addition to the flow, the rise of the peripheral diastolic pressure in all the arteries and the peripheral pulse in femoral and carotid may serve as an index of collateral extension.

The peripheral pulse and retrograde flow are elevated following increased venous return and augmented blood pressure, but may be either increased or decreased by neosynéphrine.

AUTHORS.

**Sigler, Louis H.:** Hyperactive Cardioinhibitory Carotid Sinus Reflex. A Possible Aid in the Diagnosis of Coronary Disease. *Arch. Int. Med.* 67: 177, 1941.

The normal carotid sinus mechanism is a protective adaptation to help maintain normal circulation. The adequate stimuli are changes in the intracarotid blood pressure. When the response to carotid sinus stimulation is unusually great, it is called a hyperactive carotid sinus reflex.

Hyperactivity may exhibit itself in extreme cardioinhibition, vasodepression, and cerebral manifestations.

This paper deals with an investigation of the hyperactive cardioinhibitory reflex in a series of 1,886 patients, including 1,151 males and 735 females. It was found that the reflex occurs with greater frequency and in higher degrees of response in males than in females. Its frequency and degrees of response also increase as age advances. Coronary disease is the most common condition in which the reflex occurs with the greatest frequency and the highest response. The more severe the coronary disease, the more apt the reflex is to occur and the greater its degree. Persons with other diseases and even some normal persons may present a hyperactive reflex, although not so often and to a much lesser degree.

It appears that the hyperactive cardioinhibitory carotid sinus reflex is due to lowered resistance at the synapses in the cardioinhibitory center and more so in the extracardiac and intracardiac ganglionic cells as well as in the myoneural junctions, allowing the transmission of afferent and efferent impulses in a large and at times an overwhelming volume. Coronary disease with its associated ischemia is a possible local cause for such lowering of resistance. An abnormal constitutional state and some defect in the nervous system may be other causes.

In view of the great frequency of a hyperactive reflex in coronary disease, it is recommended as a possible aid in the diagnosis of such disease in persons of the arteriosclerotic age who show suspicious signs or symptoms. It is also suggested that this reflex receive more study, since additional knowledge may help to explain the various cardiac arrhythmias and sudden, hitherto unexplained death.

AUTHOR.

**Paterson, J. C.:** Some Factors in the Causation of Intimal Haemorrhages and in the Precipitation of Coronary Thrombi. *Canad. M. A. J.* 44: 114, 1941.

The evidence supporting the hypothesis that the common cause of coronary thrombosis is an intimal hemorrhage is reviewed. Intimal hemorrhages are shown to result from the rupture of capillaries which are derived from the coronary lumen.

Some of the factors that are concerned in the rupture of intimal capillaries have been studied, and the results reported.

It is shown that increased intracapillary pressure, due to persistent hypertension, is a major factor in the formation of intimal hemorrhages and in the precipitation of coronary thrombi. As transient hypertension due to violent physical exertion or emotion will have a similar effect, these activities should be avoided by patients with coronary artery disease. This conclusion agrees with present-day clinical opinion.

The relation of vitamin C deficiency to the incidence of coronary thrombosis has been studied, and from the available evidence it is suggested that increased capillary fragility due to inadequate blood concentration of this vitamin may be concerned in the causation of some cases of coronary thrombosis. It is therefore recommended that patients with coronary artery disease be assured of an adequate vitamin C intake.

Finally, it is suggested that the calcification of atherosclerotic plaques may protect against intimal hemorrhages and coronary thrombosis. An ample calcium intake is therefore also recommended for patients with coronary artery disease.

The statistical data reported here, particularly those concerning blood plasma vitamin C concentrations, are admittedly insufficient for any definite conclusions to be drawn; they are being presented now only because the further study has been postponed indefinitely.

AUTHOR.

Weiss, Morris M.: *Coronary Occlusion in the Negro*. New International Clin. 4: 201, 1940.

This study indicates that there is no relative difference in the incidence of coronary occlusion in the negro and white races when such factors as social status and hypertension are considered. Coronary occlusion with myocardial infarction was found in 4.2 per cent of the negro and in 5.2 per cent of the white patients, 30 years and over, autopsied at the Louisville City Hospital from 1930 through 1938. This hospital is a municipal institution and admits only indigent individuals of both races. Coronary occlusion was found in 11.5 per cent of the negro and in 14.6 per cent of the white cases who had hypertension. Coronary occlusion in the absence of hypertension is rare in the negro and uncommon in the white patients autopsied at this hospital.

AUTHOR.

Gunter, J. U.: *Thrombosis of the Pulmonary Artery in Identical Twins*. Arch. Path. 31: 211, 1941.

Thrombosis in one of the main branches of the pulmonary artery is reported in each young identical twin. It is suggested that the thrombosis in the pulmonary arteries probably followed embolism from small thrombosed veins in the region of the infected middle ear in one twin and the region of the mastoid process in the other, even though such thrombosed veins were not demonstrated at autopsy.

AUTHOR.

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*\*Executive Committee.*

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## Original Communications

### THE ASSOCIATION OF GALL BLADDER DISEASE AND OF PEPTIC ULCER WITH CORONARY DISEASE; A POST-MORTEM STUDY

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ALBERTO C. TAQUINI, M.D., AND PAUL D. WHITE, M.D.  
BOSTON, MASS.

IT HAS long been known that a striking improvement in the symptoms of coronary insufficiency (angina pectoris) may follow the removal of a diseased gall bladder. Babcock<sup>1</sup> was among the first to recognize this apparent relationship, and he, among others,<sup>2</sup> believed that cholecystitis could in some instances even cause heart disease and, occasionally, congestive failure. Mayo and Straus and Hamburger<sup>3</sup> have reported (and we too have observed) subsidence of certain cardiac arrhythmias after the removal or drainage of a troublesome gall bladder, and Osler<sup>4</sup> was of the opinion that patients might die of cardiac standstill during severe biliary colic. Further evidence of the possible deleterious effects of disease of the gall bladder upon the function of the heart has been recorded electrocardiographically by Fitz-Hugh and Wolferth.<sup>5</sup> In six patients with symptoms suggestive of coronary insufficiency and abnormal (inverted) T waves in the electrocardiogram, the removal of gall stones was followed by an improvement in the cardiac symptoms and a return of the T waves to the upright position. Also, certain experimental evidence bearing upon this apparent relationship has been presented by Buchbinder and others,<sup>6</sup> who found that in icteric animals a reflex mechanism from distended biliary passages caused cardiac arrhythmias and heart block, probably by way of the vagus nerve.

Two years ago our interest in the relationship of gall bladder disease and also of peptic ulcer to disease of the coronary arteries was stimulated by the experimental work of Hall and his co-workers.<sup>7</sup> In dogs they showed that the daily administration of acetylcholine frequently

<sup>1</sup>Presented at the Sixteenth Annual Meeting of the American Heart Association, June 7, 1940.

<sup>2</sup>From the Cardiac Clinics and Laboratory and the Pathological Department of the Massachusetts General Hospital.

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produced thrombosis of the coronary arteries which in many instances was associated with (1) abnormal thickening of the gall bladder and (2) ulcers in the stomach and small intestine. Furthermore, long continued electrical stimulation of the vagus nerve in their animals produced similar results.<sup>8</sup> It was this experimental production of combined structural alterations in the coronary arteries, in the gall bladder, and in the gastrointestinal tract that caused us to re-examine the post-mortem records of the Massachusetts General Hospital for evidence of a comparable association in man, and to make a clinical survey of a large group of cases of coronary disease from this same standpoint.

In a clinical study of 1,000 patients with coronary disease, all of whom were seen in private consultation, we found clear evidence of gall bladder disease in sixty-eight (6.8 per cent), and of peptic ulcer in an additional twenty-seven (2.7 per cent); a state of vagotonia (as manifested chiefly by heart rate, A-V conduction time, and irritable gastrointestinal tract) was not preponderant in this series of 1,000 cases.

The protocols of 2,737 complete autopsies on persons 20 years, or more, of age, between Feb. 1, 1925, and Jan. 31, 1938, were examined. A simple classification of this material, as shown in Table I, seems the most satisfactory approach. There were 576 patients (21 per cent) with atherosclerosis of the coronary arteries of sufficient degree to be considered grossly abnormal. There were 456 patients (16 per cent) with structurally abnormal gall bladders. In 122 instances (4 per cent), both coronary disease and gall bladder disease were noted in the same person. Peptic ulcer occurred in 149 (5 per cent) of the total series of 2,737 cases.

A study of the significance of these data, with due consideration for the modifying effects of age and sex, is the basis of this report.

In analyzing our material we encountered a borderline group which was difficult to classify because of relatively slight, but abnormal, structural changes. We consider these minimal alterations in structure as of uncertain significance. Therefore, in the final analysis the chance of error is less if we confine our conclusions to a comparison of the definitely normal group, on the one hand, with the definitely abnormal group, on the other. For future reference, however, we have included in the tables, and designated as such, this intermediate borderline group.

The cases were classified as follows:

1a. No coronary disease.

1b. Coronary "disease" of *slight degree* was considered present in those with minimal atherosclerosis and without evident constriction of the arterial lumen. In this group the extent of atherosclerosis was too slight to be considered definitely significant, and hence these cases were set apart as a borderline group and labeled "minimal atherosclerosis."

TABLE I  
POST-MORTEM OBSERVATIONS  
(2,737 PATIENTS)

	NORMAL CORONARY ARTERIES (1,222 CASES)				MINIMAL ATHEROSCLEROSIS (939 CASES)				CORONARY DISEASE (576 CASES)			
	20-39	40-59	60 PLUS	TOTAL	20-39	40-59	60 PLUS	TOTAL	20-39	40-59	60 PLUS	TOTAL
AGE												
Normal gall bladder (2,193 cases)	397	497	161	1,055	68	310	334	712	5	124	297	426
Minimal cholesterosis (88 cases)	4	15	6	25	3	18	14	35	0	7	21	28
Gall bladder disease (456 cases)	26	78	38	142	6	73	113	192	1	23	98	122

1c. Coronary disease of *moderate to marked* degree was considered present in those with well-advanced atherosclerosis and demonstrable narrowing of the arterial lumen; the latter varied in degree from slight constriction to complete occlusion. Approximately 10 per cent were also included here because of extreme sclerosis and rigidity of the vessel wall, even though actual constriction was not recognized. More than half had calcium deposits in the vessel walls. This represents the group designated "coronary disease," and used in this report for a comparison with the strictly normal group.

2a. No gall bladder disease.

2b. Gall bladder "disease" of *slight degree* included those who showed, post mortem, slight or even moderate cholesterosis, but no stones. Alteration of this degree was held by us to be of uncertain significance, and hence was set apart with the designation "minimal cholesterosis." This group was not considered in the final comparison.

2c. Gall bladder disease of *moderate to marked* degree included those with or without an abnormally thickened gall bladder which contained one or more stones. Approximately 5 per cent were included because of extreme thickening of the wall, even though stones were absent. Whether or not one is justified in considering the presence of stones, per se, as always indicating gall bladder disease is open to question. However, there appeared to be less chance of error in arbitrarily including all, rather than attempting to exclude some. In twenty instances (4 per cent), cholecystectomy had been performed. These were included in the belief that the operation had been indicated. This then represents the group (456 in number) which we have called "gall bladder disease."

3. *Peptic ulcer* offered less difficulty in classification. It was considered to have been present in all who had evidence of either an active or a well-healed lesion in the stomach or duodenum. None was of the agonal (terminal) type.

#### DISEASE OF THE GALL BLADDER AND CORONARY ARTERIES

In the group of 576 patients with coronary disease, the added complication of gall bladder disease occurred in 122, or 21 per cent (Table I), whereas, in the 1,222 patients with normal coronary arteries, gall bladder disease was noted in only 142, or 11.5 per cent. Furthermore, this apparently significant association is still evident if we consider (from a slightly different approach) the incidence of coronary disease in the total group with gall bladder disease, since this includes 192 additional instances of gall bladder disease which were noted in those with "minimal atherosclerosis," and hence were not considered in the first comparison. Thus, the gall bladder disease which was present in a total of 456 cases was complicated by coronary disease in 122, or 27 per cent, in contrast to an incidence of 19 per cent in those without gall bladder disease (426 in a total of 2,193 cases).

These rather broad comparisons suggest a slight, but apparently significant, tendency for gall bladder disease and coronary disease to occur in the same person. However, the possibility that certain modifying factors, such as age and sex, may have distorted our analysis warranted further scrutiny.

When one compares this association in males and in females the same general trend is still evident. As shown in Table II, there were 415 men with coronary disease, sixty-nine of whom had abnormal gall bladders (16 per cent), in contrast to an incidence of 8 per cent (sixty-one instances) of abnormal gall bladders in the 710 men with normal coronary arteries. A similar comparison among the women indicates that, of the 161 with coronary disease, fifty-three (33 per cent) also had abnormal gall bladders and, of the 512 women with normal coronary arteries, only eighty-one (16 per cent) had gall bladder disease.

In accord with clinical observation, gall bladder disease occurred in this post-mortem study more often in women (22 per cent) than in men (12 per cent), and, as was also to be expected, the reverse was true with regard to the incidence of coronary disease, which was present in 37 per cent of the males as compared to 24 per cent of the females, excluding the intermediate group with minimal atheroma.

It is interesting to observe that, in spite of this apparent tendency for the two conditions to occur in the same person, in those under the age of 40 (Table I) there was less of an association than in the group as a whole and there was a considerable increase in both with each successive decade. Statistical tests made by Dr. E. B. Wilson, of the Department of Statistics, School of Public Health, Harvard University, have confirmed the impression that the increasing incidence of gall bladder disease and of coronary disease after 20 years of age did not surpass the increment expected with mounting numbers in each group. The coincidence of the two conditions in the same individuals is, however, not to be accounted for by age alone; there remain some factor or factors that need further elucidation.

#### PEPTIC ULCER AND CORONARY DISEASE

Peptic ulcer was found in a total of 149 instances in this post-mortem series, an incidence of 5 per cent. Well-marked coronary disease was a complication in thirty patients (20 per cent), whereas sixty-eight (45 per cent) had entirely normal coronary arteries. This same incidence of coronary disease was noted in the remaining 2,588 patients without peptic ulcer; 546 (21 per cent) had definite coronary disease and 1,154 (45 per cent) had none. This apparently negative relationship between peptic ulcer and coronary atherosclerosis is further illustrated in Table III. Here it is apparent that peptic ulcer occurred in thirty (5 per cent) of the 576 patients with coronary disease, and with equal frequency (sixty-eight, or 5.5 per cent) among 1,222 patients



TABLE II  
RELATION TO SEX AND AGE

AGE	NORMAL CORONARY ARTERIES (1,222 CASES)				MINIMAL ATHEROSCLEROSIS (939 CASES)				CORONARY DISEASE (576 CASES)			
	20-39	40-59	60 PLUS	TOTAL	20-39	40-59	60 PLUS	TOTAL	20-39	40-59	60 PLUS	TOTAL
<i>Males (1,767 Cases)</i>												
Normal gall bladder (1,481 cases)	221	300	117	638	52	224	241	517	5	104	217	326
Minimal cholesterosis (49 cases)	1	7	3	11	1	9	8	18	0	4	16	20
Gall bladder disease (227 cases)	11	30	20	61	1	36	60	97	0	15	54	69
<i>Females (980 Cases)</i>												
Normal gall bladder (712 cases)	176	197	44	417	16	86	93	195	0	20	80	100
Minimal cholesterosis (39 cases)	3	8	3	14	2	9	6	17	0	3	5	8
Gall bladder disease (229 cases)	15	45	18	81	5	37	53	95	1	8	44	53

TABLE III  
PEPTIC ULCER

AGE	NORMAL CORONARY ARTERIES (1,222 CASES)				MINIMAL ATHEROSCLEROSIS (939 CASES)				CORONARY DISEASE (576 CASES)			
	20-39	40-59	60 PLUS	TOTAL	20-39	40-59	60 PLUS	TOTAL	20-39	40-59	60 PLUS	TOTAL
<i>Males (1,757 Cases)</i>												
Peptic ulcer (118 cases)	8	32	11	51	4	19	16	39	1	9	18	28
No ulcer (1,639 cases)	226	304	129	659	50	250	293	593	4	114	269	387
<i>Females (980 Cases)</i>												
Peptic ulcer (31 cases)	4	13	0	17	0	4	8	12	0	1	1	2
No ulcer (949 cases)	190	240	65	495	23	128	144	295	1	30	128	159

without coronary disease. The majority, fifty-one of the eighty-one patients with peptic ulcer (63 per cent), had the least coronary disease, which, in turn, emphasizes further the lack of association between ulcer and coronary heart disease. In accord with clinical experience, most of the ulcers were in men (118). Since the proportion of males to females in the total series was 1,757 to 980, the relative frequency of ulcer in men as compared to women in this series was approximately 2 to 1.

#### DISCUSSION

The results of this study, supported by statistical tests, are in agreement with those of previous workers<sup>9</sup> who have failed to find evidence from post-mortem investigation that diseases of the gall bladder and of the coronary arteries are closely related except through the occurrence of an unknown "aging" factor.

Clinical experience, however, indicates that a troublesome gall bladder or peptic ulcer may seriously disturb cardiac function in the presence of otherwise silent coronary disease. Disturbed functions in other organs may also act in the same way, but disease of the upper gastrointestinal tract and of the gall bladder appears to have a more profound effect, probably because of the proximity of the respective nerve pathways in the spinal cord and of related activities of vagal reflexes.

We have been unable to assemble evidence from this post-mortem survey to suggest the occurrence in man of a close association between disease of the gall bladder and upper intestinal tract and disease of the coronary arteries which is comparable in any degree to the important structural alterations produced experimentally in dogs by acetylcholine or through vagal stimulation.

Since the completion of this report, Breyfogle<sup>10</sup> has published the results of his studies concerning the coexistence of gall bladder and coronary artery disease. In a series of 1,493 autopsies he found an even more positive association than ours between disease of the gall bladder and that of the coronary arteries. The differences between his findings and ours are to be accounted for, in large part at least, by the higher proportion of young persons and of women in his group.

#### CONCLUSIONS

From a study of the records of 2,737 post-mortem examinations of adult patients, it has been shown that:

1. Gall bladder disease occurred almost twice as often in patients with coronary disease as in those with normal coronary arteries. Some factor or factors related, in part at least, to an aging process but as yet not definitely elucidated are apparently responsible for this finding.

2. There was no indication of a significant association of peptic ulcer and coronary disease in the same person.

3. In contrast to the important structural alterations simultaneously produced experimentally in the gall bladder, in the upper intestinal tract, and in the coronary arteries of animals, as previously reported, no conclusive evidence of a comparable association in man was apparent from the present study.

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# DISCUSSION

DR. PAUL D. WHITE, Boston.—I would like to emphasize very briefly two important points in this study of the correlation or association of gall bladder disease and coronary disease. The first concerns the low incidence of both conditions together in the younger patients. For example, of twenty-seven patients with severe gall bladder disease under the age of 40, twenty-six had normal coronary arteries; only one had coronary disease of moment; whereas, of six patients with coronary disease of considerable moment under the age of 40, five had normal gall bladders and only one had gall bladder disease.

The second point concerns the greater frequency with which gall bladder disease is found in women than in men, and the greater frequency of coronary disease in men than in women at earlier ages.

These facts indicate that whatever mechanism is producing coronary disease in young people is not at the same time producing gall bladder disease, and vice versa.

DR. ERNST P. BOAS, New York.—This valuable study has interested me in particular because for some years Dr. Hyman Levy and I have devoted some attention to the association of peptic ulcer and coronary disease. At first we had the impression that these two conditions frequently occurred together, but a more complete review of our clinical material gives results corresponding to those of Dr. Walsh, Dr. Bland, and Dr. White.

However, there are certain phenomena which suggest that in individual cases there is a causal relationship between these two conditions. I refer to cases, which are not so very rare, in which coronary thrombosis and an acute, penetrating, peptic ulcer apparently occur simultaneously. I have seen a number of such cases in which the diagnosis of cardiac infarction was confirmed by the electrocardiogram and the penetrating ulcer was demonstrated roentgenologically, in which the symptoms of the two conditions were difficult to distinguish from one another. Here I am not referring to the well-known cardiac infarction that occurs as a result of severe hemorrhage from an ulcer, but to cases in which there was a simultaneous onset of pain in the epigastrium and in the chest with various types of radiation.

Second, there are patients with angina pectoris who have or develop peptic ulcer, in whom the anginal pain develops an ulcer timing. Instead of having the anginal pain predominantly on exertion, these patients are likely to get the anginal pain an hour or so after meals, and are frequently relieved by alkalies.

The analysis of this clinical picture is difficult because of the cross radiation of pain when these two conditions are associated, and because the respective symptoms become so closely intermixed. For instance, if a patient first has a peptic ulcer and then develops angina pectoris, he may have typical anginal pain on exertion, and then, when he gets his ulcer pain after eating, it will be felt in the precordium instead of in the epigastrium and will radiate down the left arm.

I fully realize that these scattered observations do not represent a tremendous mass of material nor prove any definite etiological relationship between the two conditions. However, we must keep in mind that cardiac infarction may arise through different types of pathologic processes and that it is quite conceivable that in certain instances the same arterial disease or the same arterial insult may manifest itself simultaneously in a coronary artery and in a gastric artery.

We concede that gall bladder disease and coronary disease are not frequently related, yet in cases such as those described by Fitz-Hugh and Wolferth there seems to have been a very direct relationship.

Although the statistical analysis made in this paper disproves a direct relationship between peptic ulcer, gall bladder disease, and coronary disease in the majority of instances, we must not conclude that there is never any relationship, but recognize that further intensive study may bring out common factors in some of these cases which so far have escaped recognition.

## A COMMON ELECTROCARDIOGRAPHIC VARIANT FOLLOWING ACUTE MYOCARDIAL INFARCTION—THE $T_N$ TYPE

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CHICAGO, ILL.

IT HAS now been definitely established by careful correlation of clinical, electrocardiographic, and anatomical findings that acute myocardial infarctions produce a series of changes in the contour of the electrocardiogram, in a large percentage of cases, which are helpful in diagnosis. Soon after Herrick<sup>1</sup> called attention to the clinical picture of coronary thrombosis, Smith<sup>2</sup> described the electrocardiographic changes found in acute myocardial infarction in the experimental animal, and Pardee<sup>3</sup> those in a patient. Since then a large and well-founded literature on this subject has appeared.<sup>4-18</sup> Parkinson and Bedford<sup>4</sup> first pointed out two particularly characteristic patterns which may occur: The  $T_1$  type, in which the T wave in Lead I becomes inverted, and the  $T_3$  type, in which the T wave in Lead III becomes inverted; classically the S-T segment and T wave of Leads I and III present a reciprocal appearance as far as direction is concerned. Wilson and his co-workers<sup>5</sup> indicated that changes in the initial ventricular deflection are also common, a Q pattern tending to appear in the same lead in which the T wave becomes inverted. Barnes and Whitten<sup>6</sup> attempted to correlate the electrocardiographic pattern with the location of the infarction as demonstrated at autopsy; they found that the  $Q_1T_1$  type occurred when the anterior surface of the left ventricle was infarcted, and the  $Q_3T_3$  type when the posterior surface of the left ventricle was thus involved.

These fundamental contributions have gained general acceptance, and are quoted in most textbooks on electrocardiography. It is unfortunate, however, that too often they have been stressed as being the sole criteria for the electrocardiographic diagnosis of acute myocardial infarction. Unless the above criteria are amplified, the electrocardiograph becomes an inefficient diagnostic instrument, and may even conceivably become a dangerous one. Four additional considerations must be taken into account; they are: (1) The electrocardiogram following an acute myocardial infarction has as a major characteristic a tendency to change serially over a relatively short period, i.e., over the course of days or weeks. (2) The chest leads may bring out evidence of this condition, not uncommonly in the absence of diagnostic limb lead changes. (3) The entire record may show either non-diagnostic or, for a time at least, no changes following an acute myo-

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cardial infarction, and (4) The changes in the electrocardiogram after acute myocardial infarction may follow a pattern which differs from those widely accepted as classical. The first two considerations have already received extensive attention in the literature,<sup>7-10, 11-14</sup> and the third might well deserve it.<sup>15-18</sup> It is with the fourth, however, that this communication is concerned.

In this Heart Station we have found it to be the exception rather than the rule for serial records following coronary occlusions to show the pure, classical  $Q_1T_1$  or  $Q_3T_3$  changes. Among the many records which stray from the typical, we have been struck by the frequency of a pattern which deserves greater mention than it has hitherto received. This group of cases is characterized by the occurrence, at some time or another during the evolution of the electrocardiogram following acute myocardial infarction, of T waves which are simultaneously inverted in all three of the standard limb leads. Because the T wave in all three leads is negatively directed, we call this the  $T_x$  pattern<sup>19</sup> to conform with the nomenclature in common use. In this communication all the  $T_x$  records in recent myocardial infarctions in our files are assembled for analysis.

#### SELECTION OF CASES

The records of all cases listed under "acute myocardial infarction" in the Heart Station files since 1930 were examined. Of this group those cases which showed an inverted T wave in all three limb leads at some stage in their evolution were chosen for this study. The clinical histories of the latter were then collected and correlated with the electrocardiographic records. Those cases in which the electrocardiographic evolution and/or the clinical evidence indicated beyond reasonable doubt that an acute or healing myocardial infarction was present were selected for this presentation; the others were discarded.

Our criterion for T wave negativity was simply that the T waves be inverted; no particular configuration was demanded. In many cases the inverted T waves were of the so-called "coronary" contour in all three leads (Figs. 5, 7), in some cases only in one or two of the leads (Fig. 4), and rarely in none (Fig. 1).

#### OBSERVATIONS

Out of a total of 743 cases of myocardial infarction listed in our files since 1930, sixty showed a  $T_x$  pattern at some time or another during the electrocardiographic evolution, an incidence of 8.1 per cent. However, we adopt a very conservative attitude and suggest the diagnosis of recent coronary occlusion whenever the electrocardiogram is even slightly suspicious, and such a record is automatically indexed in the files as an infarction. Further study often disproves the diagnosis, but the initial indexing is not cancelled. Analysis indicated that only 380 of the 743 cases conformed to the same criteria which we set

up for the 60 records accepted for this report. Using the corrected figures we found that 15.8 per cent of the cases proved beyond reasonable doubt to be acute myocardial infarctions showed a  $T_N$  pattern at some stage during their electrocardiographic evolution. We realize that the pattern we are describing represents a purely artificial classification, and that an accurate statistical analysis, therefore, has no particular significance. The above figures are quoted only to bring out the fact that the  $T_N$  type is a not infrequent occurrence.

The age of the patients varied from 34 to 77, the average age being 57.2 and the mean age 58. Forty-four of the patients were males and 16 females. Seven of the 60 patients came to autopsy. Three of these have been previously illustrated in the literature. The records of three of the other four cases are shown in Figs. 1-3, and the data on all seven are summarized in Table I.

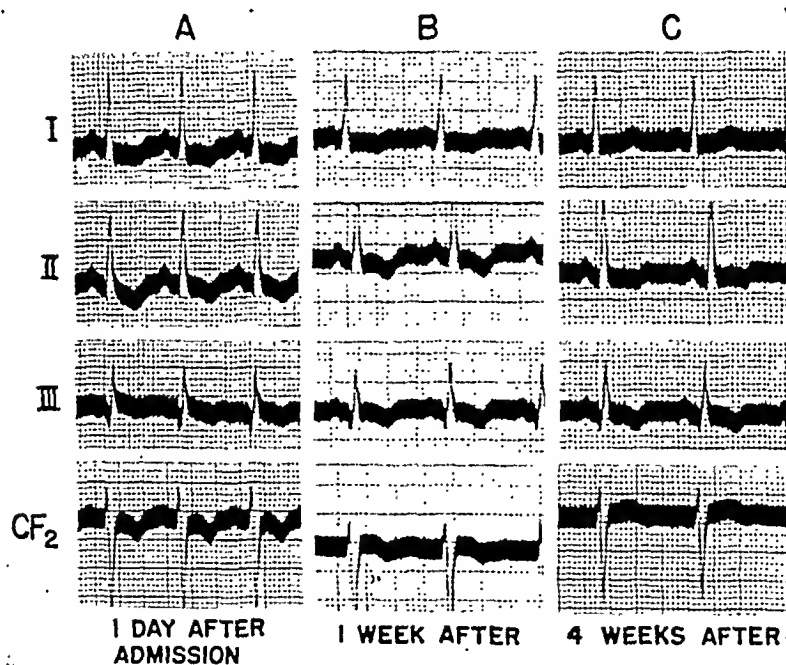


Fig. 1.—This patient, a female, aged 40, entered the hospital with a history of substernal pain for four weeks, especially severe the latter two weeks, and not relieved by nitroglycerin. The changes between the first two records, both of which may be classed as  $T_N$ , suggest that an infarct had occurred. The diagnosis is confirmed by the changes seen in record C. The patient re-entered the hospital eight months later in a comatose condition and died within 24 hours. At post-mortem examination there were found, in addition to a recent infarction of the left ventricle, two healed infarcts. One, measuring 9 cm. in diameter, involved the septum and posterior wall of the left ventricle, the other, in the anterior apical region, measured 1.5 cm. The most probable explanation for the  $T_N$  pattern in this case is that the anterior wall infarction was in the healing stage at the time of the first hospitalization, while the posterior wall infarct had been present previously, as indicated by the persistent  $QsTs$ . The combination produced inverted T waves in all three limb leads.

These sixty cases constitute a heterogeneous group. In some the  $T_N$  character appeared at the onset (Fig. 3), in others at a later stage in healing (Fig. 5). In some this represented a transitory finding (Fig. 4), in others it was more protracted (Fig. 7). In many of the records we could identify a pattern which permitted us to presumptively localize



the infarction. This may have been done through the presence of a particular Q pattern (Fig. 5), through the appearance of the chest leads (Fig. 4), or through the development, either before or after the  $T_N$  stage, of a characteristic  $T_1$  or  $T_2$  type (Fig. 7). In many records, however, we were unable to do so, because evidence was either lacking or conflicting (Fig. 2).

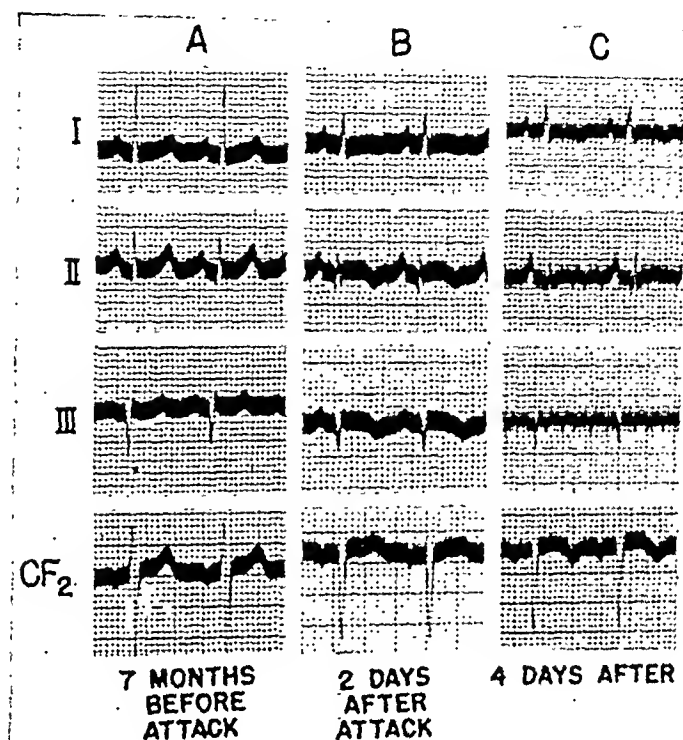


Fig. 2.—This patient, a female, aged 50, entered the hospital, one hour after an attack of severe epigastric pain. The record taken 2 days later, showing a  $T_N$  pattern, indicated that an acute myocardial infarction had occurred, and the last record (deformed by a 60 cycle artefact) confirmed the diagnosis. The patient died six days later. At post-mortem examination a recent infarct of the posterolateral wall of the right ventricle and posterior portion of the interventricular septum was found, and also an old healed infarct of the anterior apical portion of the left ventricle. No evidence of pericarditis was seen. There are two possible explanations for the  $T_N$  pattern in this case. One is the atypical location of the acute infarct, i.e., in the right ventricle. The second is the involvement of both posterior and anterior walls. The changes seen in Lead CF<sub>2</sub> support the latter concept, even though anatomically only an old infarction was found anteriorly. However, we are unable to say which of the two mechanisms is primarily responsible.

#### DISCUSSION

We subjected all the  $T_N$  cases to close study in an attempt to explain the reason for its occurrence, and discovered that there are at least seven possible mechanisms which may be responsible.

1. Acute infarction may involve both the anterior and posterior walls of the left ventricle either by separate involvement of these two areas, or by a massive infarction which involves both together by confluence or extension. In either case there is a tendency for both  $T_1$  and  $T_2$  types to develop, so that the composite may show any combination of these two types. Under fortuitous circumstances a  $T_1$  type may result (Fig. 3).

2. Acute infarction may occur in the presence of pre-existing coronary insufficiency, either with or without a previous infarction. Recent investigations<sup>20, 21</sup> strongly suggest that a relatively sudden occlusion in one coronary artery could produce ischemia in one area to the point of infarction, while producing a lesser degree of ischemia in another area not adjacent. From the latter, injury currents may arise, even in the absence of anatomical evidence of infarction,<sup>22</sup> and summate with those from the acutely infarcted area to produce a  $T_N$  pattern (Fig. 1).

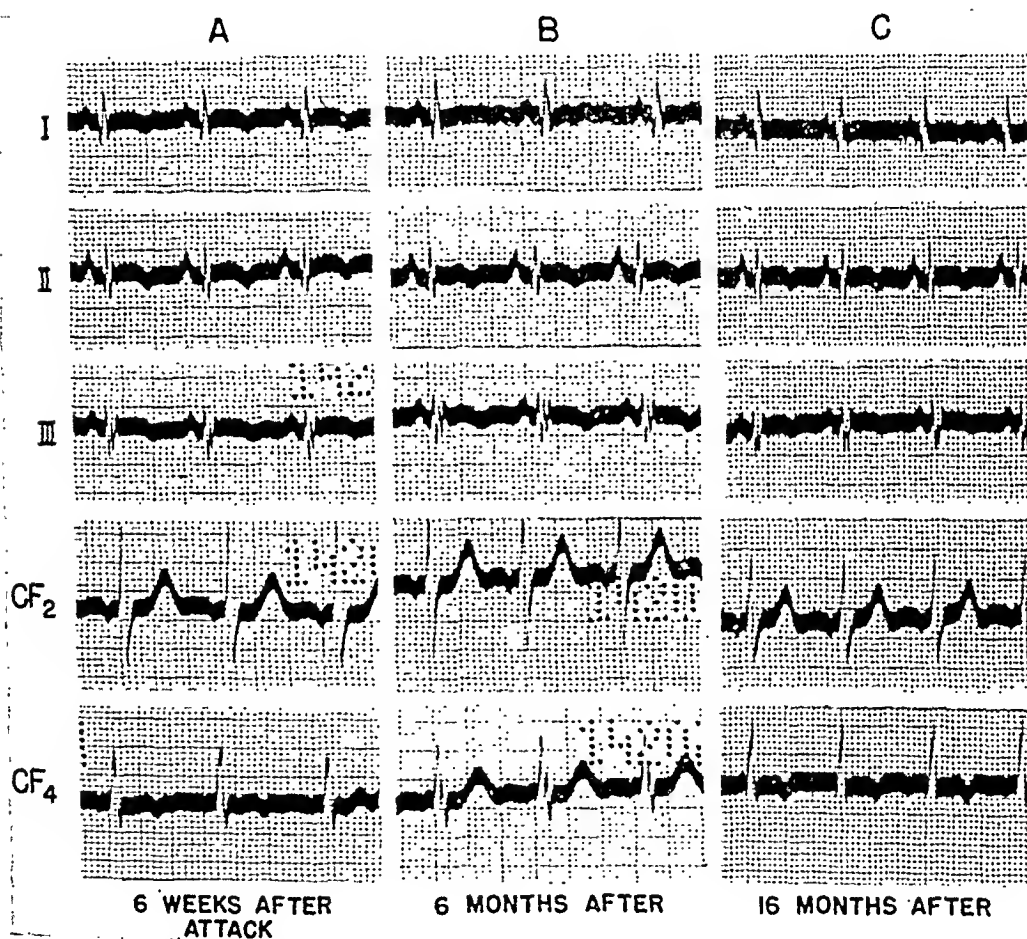


Fig. 3.—This patient, a female, aged 50, had an attack clinically diagnosed as an acute coronary occlusion and had been kept at home in bed for six weeks before the first electrocardiogram. The third record was taken when she entered the hospital for an unrelated surgical condition, of which she died one week later. At post-mortem examination a healed infarct was found, involving the apex, lateral wall, and posterior surface of the left ventricle. On the posterior surface, the wall was thinned out over an area approximately 2 cm. in diameter, and overlying this was a patch of adherent pericardium. In this instance the simultaneous involvement of two surfaces produced a  $T_N$  pattern.

3. Pericarditis may by itself affect the electrocardiogram to the point of producing inverted T waves of the so-called "coronary" contour in all three limb leads.<sup>23-25</sup> When complicating an acute myocardial infarction, therefore, diffuse pericarditis may produce a

$T_N$  pattern (Fig. 5). When localized to the area of infarction, however, pericarditis should not disturb the pattern produced by the infarct itself.<sup>26</sup>

4. An acute posterior wall infarction of the  $T_2$  type may occur in a patient whose electrocardiogram previously showed evidence of preponderant hypertrophy of the left ventricle in which  $S-T_1$  is depressed and  $T_1$  inverted. In such a case  $T_1$  may remain inverted, and, when  $T_2$  and  $T_3$  become inverted, a  $T_N$  pattern results (Fig. 6).

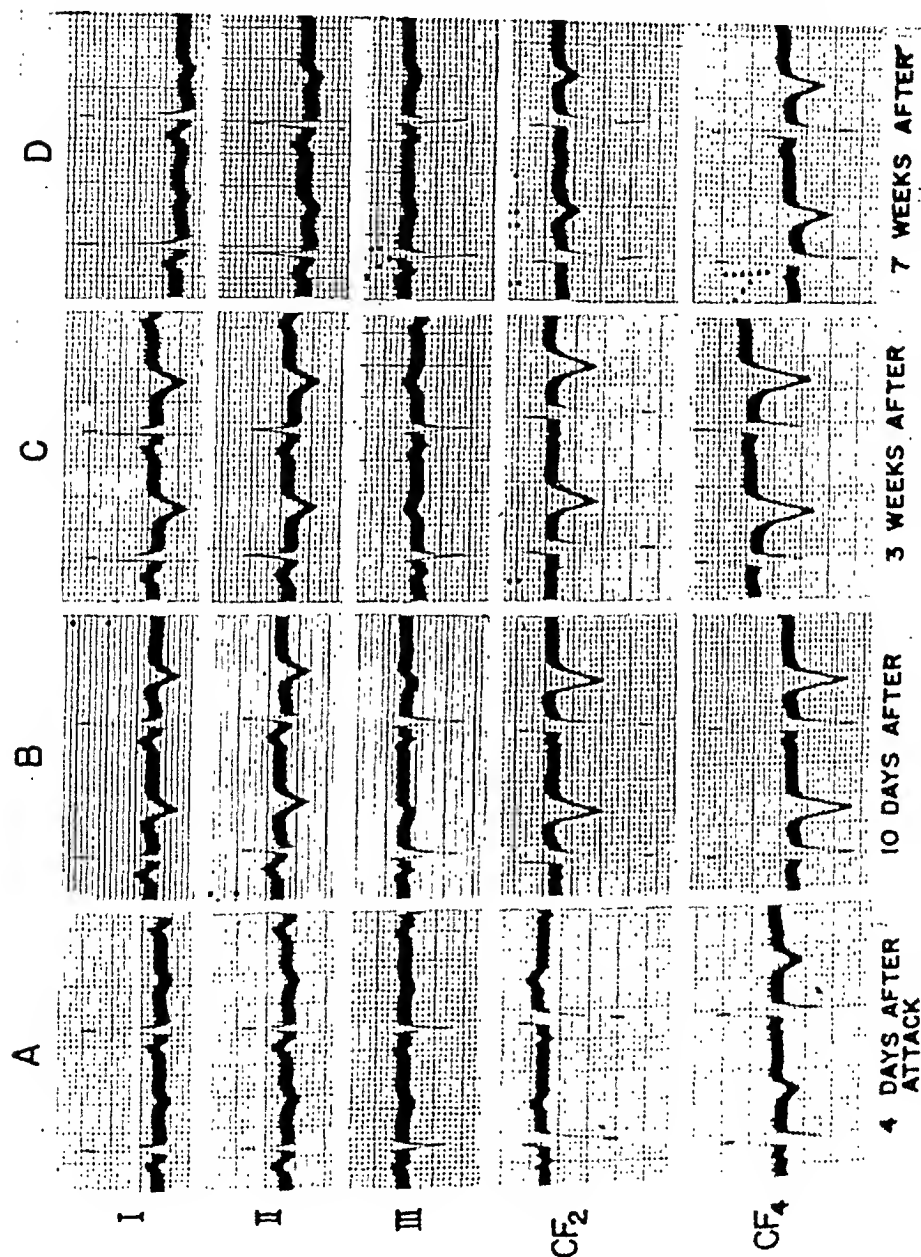


Fig. 1.—This patient, a female, aged 72, entered the hospital three days after an attack of precordial pain of one-half hour's duration, not relieved by nitroglycerin. The electrocardiographic evolution indicated the presence of an acute anterior wall infarction. Apparently  $T_2$  was inverted at the outset; it was not until the third record that the reciprocal character of Leads I and III appeared, and later  $T_2$  and  $T_3$  became inverted. This  $T_N$  inversion in this case was probably a normal or incidental occurrence, and explains the  $T_N$  pattern.

5. An acute anterior wall infarction of the  $T_1$  type may occur in a patient whose electrocardiogram previously showed an inversion of  $T_2$ . This  $T_2$  inversion may be a normal finding, may be associated with a right ventricular preponderance, or may be the residual of an old  $T_1$

(posterior wall) type of infarction; in the latter instance it could also fall into Group 2 above. In any case,  $T_3$  may remain inverted, and, when  $T_1$  and  $T_2$  become inverted, a  $T_N$  pattern results (Fig. 4).

6. An acute infarction may be located elsewhere than in the areas particularly favorable for the production of the pure  $T_1$  or  $T_3$  type. Under fortuitous circumstances this may produce the  $T_N$  pattern. Among the possible atypical locations are the lateral surface of the left ventricle and any portion of the right ventricle (Fig. 2).

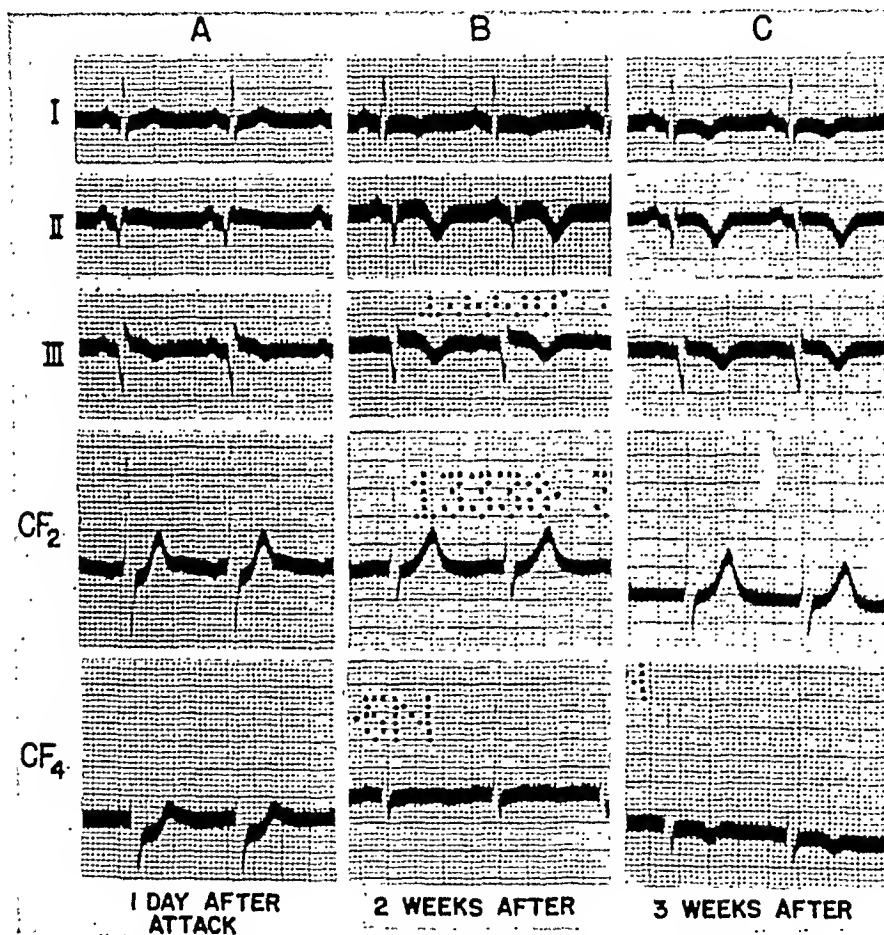


Fig. 5.—This patient, a male, aged 65, entered the hospital complaining of severe chest pain of twelve hours' duration. The first electrocardiogram showed changes typical of a posterior wall infarction. On the third hospital day a pericardial friction rub was heard. Since the infarct was located on the posterior wall of the heart, elicitation of a friction rub suggested that a diffuse, rather than localized, pericarditis was present. This would account for the  $T_N$  pattern seen in the next two records, and also for the changes seen in Lead  $CF_4$ .

7. When intraventricular block is present, the final, as well as the initial, ventricular deflection is usually abnormal in contour. This may influence the electrocardiographic pattern to such an extent that a  $T_N$  type will occur following an acute myocardial infarction.

It is possible that other mechanisms may be involved; three that may be mentioned are: (1) Digitalis administration<sup>27</sup> (2) rotation of the

heart on its long axis accompanying dilatation<sup>28</sup> (3) infarction predominantly involving certain muscle bundles, and (4) pulmonary embolism complicating an anterior wall infarction.<sup>29</sup> However, we were unable to connect any cases in our series with these latter mechanisms.

The anatomic findings in the autopsy cases of our series are presented in Table I, and in the cases collected from the English literature in Table II; in each instance an attempt is made to explain the cause of the T<sub>x</sub> pattern from the data available. These cases may not represent an accurate cross-section from which the relative frequency of the various mechanisms can be determined, because those patients that die might be expected to show multiple infarctions, and therefore no conclusions on this matter are drawn. In those patients of our series who did not come to autopsy only a few presented clear-cut evidence that one of the above-mentioned mechanisms was operating; in many instances a satisfactory conclusion could not be reached. The latter

TABLE I

AUTHORS	AUTOPSY FINDINGS		EXPLANATION FOR T <sub>x</sub> PATTERN
Saphir, Priest, Hamburger, and Katz <sup>20</sup>	Fig. 26	Anterior apical infarction with circumscribed local pericarditis.	No explanation.*
	Fig. 30	Myocardial infarctions with aneurysmal dilatation of apex and posterior wall of the left ventricle.	(1) More than one region involved. (2) Presence of intraventricular block.
Bohning and Katz <sup>10</sup>	Fig. 6B	Healed infarcts of posterior wall of left ventricle and anterior wall of left ventricle. Organizing infarct of apex of left ventricle.	More than one region involved.
This report	Fig. 1	Old infarcts in posterior wall of left ventricle and septum and in anterior apical region.†	More than one region involved.
	Fig. 2	Recent infarct of posterolateral wall of right ventricle and posterior portion of the intraventricular septum. Old infarct of the anterior apical portion of left ventricle.	(1) Atypical location—right ventricle. (2) More than one region involved.
	Fig. 3	Healed infarct involving anterior, lateral, and posterior surfaces of left ventricle. Localized pericarditis over posterior portion of the above infarct.	More than one region involved.*
	Not illustrated	Old infarct involving septum (not further specified).‡	No explanation.‡

\*A circumscribed local pericarditis should produce no changes in the electrocardiogram to disturb the pattern produced by the myocardial infarction underlying it.<sup>20</sup>

†Patient died of a recurrent myocardial infarction, evidence of which was also seen at necropsy.

‡In this case nothing found at necropsy could be used as a valid explanation.

may have been due to the fact that more than one possibility was discernible or to the fact that no clear evidence could be found. To illustrate some of the varieties which were encountered, seven typical

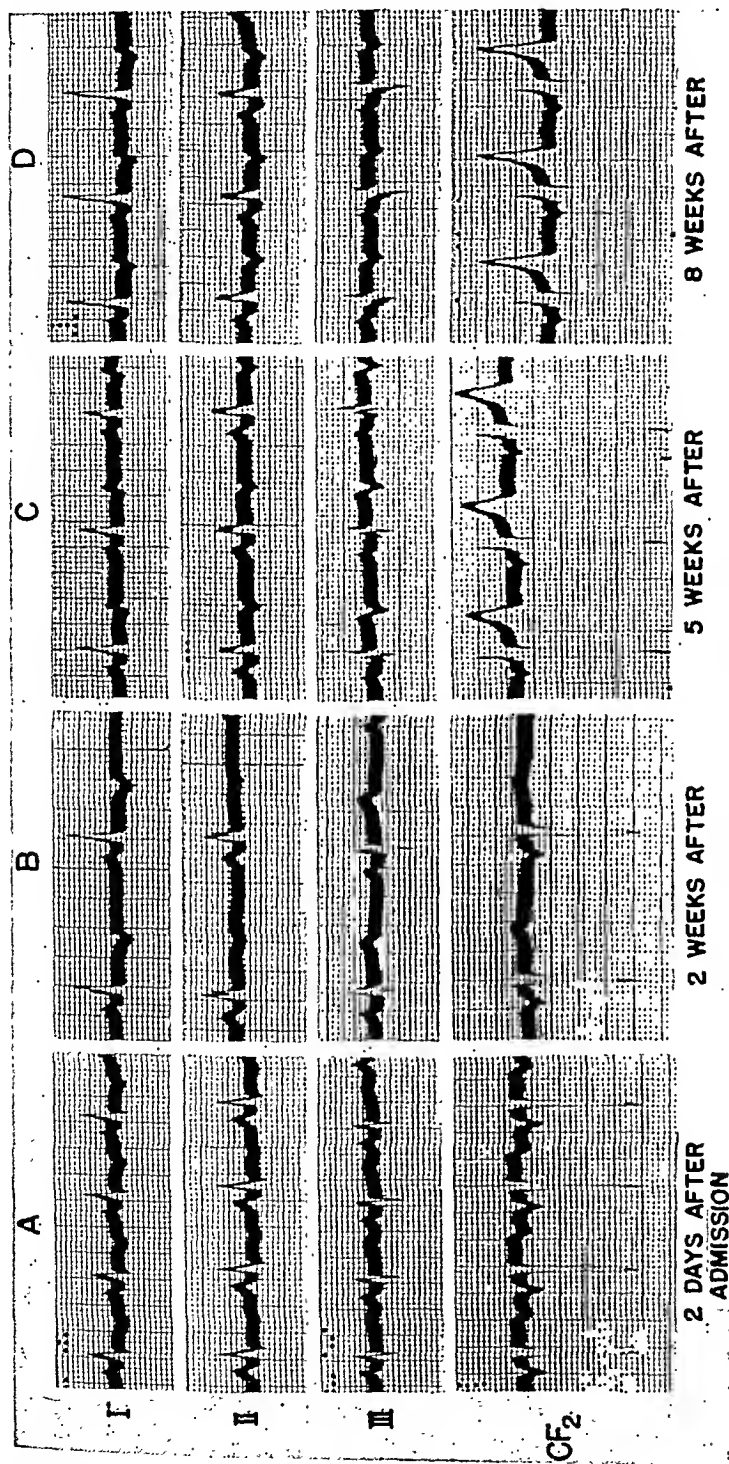


Fig. 6.—This patient, a colored male, aged 54, entered the hospital complaining of hemoptysis of one day's duration. A diagnosis of pulmonary infarction was made. He had been known to have arterial hypertension (186/110 mm. Hg) for at least two years, but denied having had any chest pain. His course in the hospital was entirely uneventful, but serial electrocardiograms revealed changes during the latter weeks typical of those seen in the healing of recent infarcts of the posterior wall of the left ventricle. Superimposed upon a record indicating left ventricular preponderance in that S-T<sub>1</sub> is depressed and T<sub>1</sub> inverted, at one stage (D) a T<sub>N</sub> pattern developed, although at an earlier stage (C) T<sub>1</sub> had become diphasic. Although post-mortem confirmation was not available, the electrocardiographic evidence in this case is definite enough to suggest a diagnosis of a "silent" myocardial infarction.

records from our series are shown in Figs. 1-7, together with a short discussion in the legend of the factors which may have operated in each case to produce the T<sub>N</sub> pattern.

GOOD  
LEXINGTON, KY.

The primary purpose of this communication is to point out that the electrocardiogram following acute myocardial infarction may not infrequently show inverted T waves in all three limb leads instead of the so-called "classical" picture of reciprocal appearance of the T waves in Leads I and III. When the T waves are found inverted in both these leads, therefore, a recent myocardial infarction should be considered, and other criteria to determine the diagnosis should be utilized.

TABLE II

AUTHORS	AUTOPSY FINDINGS		EXPLANATION FOR T <sub>s</sub> PATTERN
Willius and Barnes <sup>30</sup>	Fig. 1	Recent infarcts of upper half of intraventricular septum and of posterior basal surface of left ventricle, each 2 cm. in diameter. Organized mural thrombus at apex.	(1) Posterior wall (T <sub>1</sub> ) type of infarct superimposed on a previous left ventricular preponderance.* (2) More than one region involved.†
	Fig. 18	Recent infarct of anterior wall of left ventricle and old healed infarct of posterior portion of left ventricular septum.	(1) More than one region involved. (2) Presence of intraventricular block.
Levine <sup>31</sup>	Fig. 27	Infarction of left ventricle at apex extending over posterior surface.	More than one region involved.
	Fig. 40	Obliterated pericardial sac, aneurysm of apical portion of left ventricle with mural thrombus.	Pericarditis.
	Fig. 79	Infarct of left ventricle with mural thrombus (not further specified).	No explanation.‡
Winternitz <sup>32</sup>	Fig. 2	Aneurysm involving wall of the left ventricle, septum, and apex.	More than one region involved.
Barnes <sup>33</sup>	Fig. 1	Anterior infarction with adherent pericarditis involving all but the posterior wall of the left ventricle.	Pericarditis.
Wood, Wolferth and Bellet <sup>34</sup>	Fig. 6	Massive infarction of posterior and lateral walls and posterior portion of septum. Also large healed infarct of anterior wall.	(1) More than one region involved: (a) Massive acute infarction. (b) Recent infarction in presence of old infarction. (2) Posterior wall (T <sub>1</sub> ) type of infarct superimposed on a previous left ventricular preponderance.
Pardee <sup>35</sup>	Fig. 34	Lateral wall infarct.	Atypical location.

\*Patient was known to have had hypertension, and the patible with the pattern of left ventricular preponderance.

†Presence of organized mural thrombus is presumptive evidence in myocardium overlying it.

‡This patient had an atypical clinical attack. Nothing tracing nor in the report of autopsy findings satisfactorily the T<sub>s</sub> pattern.



Secondarily, we have presented seven different mechanisms which, acting either singly or in combination, may produce the  $T_N$  pattern.

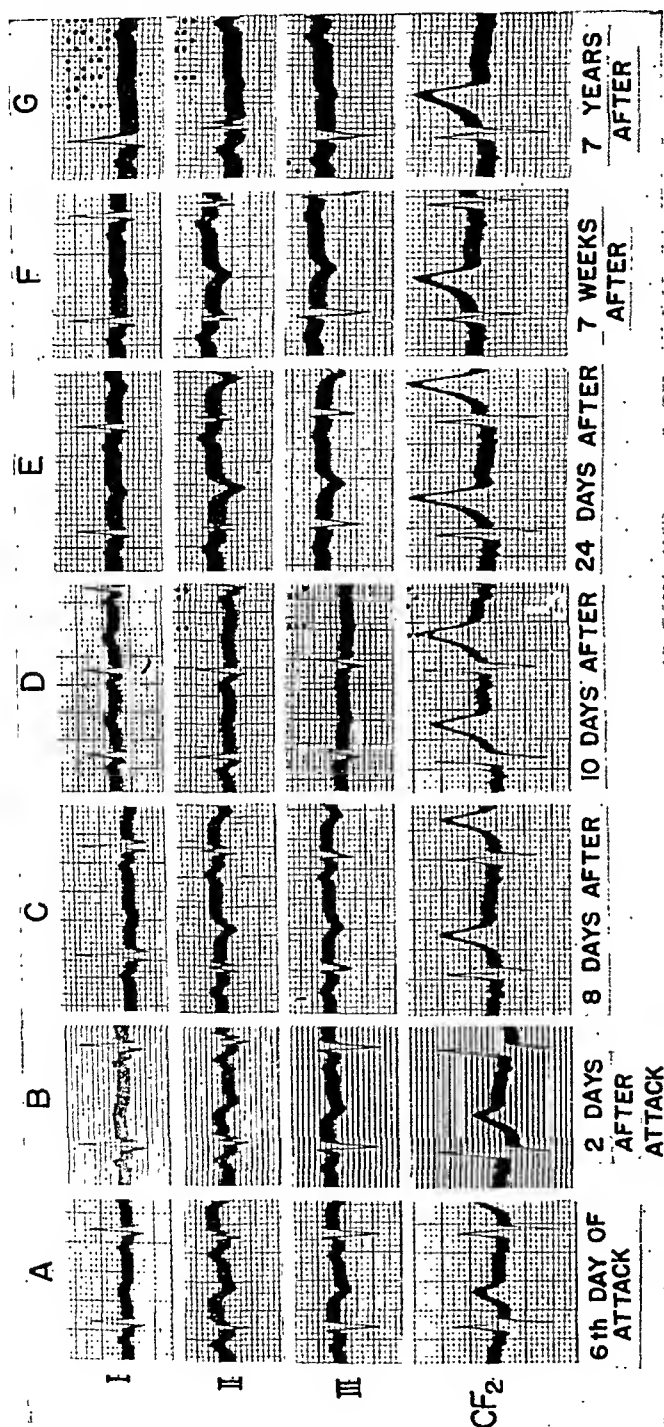


Fig. 7.—This patient, a male, aged 58, entered the hospital complaining of severe pain in the right parasternal area of five days' duration. Although no evidence of pericarditis was elicited clinically, the evolution in the first three electrocardiograms is typical for that seen in cases of acute posterior wall infarctions complicated by diffuse pericarditis. However, we are not aware of evidence indicating that the phenomenon seen in record D, i.e., temporary reversal of an inverted T wave to upright, is characteristic of the electrocardiographic evolution in pericarditis. An alternative explanation would assume that anterior wall involvement was present in addition to that on the posterior surface. The persistent  $Q_1$  tendency lends support to this possibility, and in the healing stages of myocardial infarctions we have seen transitory reversals in the direction of the T wave.<sup>33</sup>

Barnes<sup>33</sup> has suggested that the diagnosis of pericarditis complicating infarction could be made when this electrocardiographic picture was seen. However, examination of the autopsy cases in Tables I and II



shows that in twelve of the sixteen no evidence of pericarditis was described at post-mortem examination. This lends weight to our interpretation of the multiple mechanisms involved in those patients of our series who did not come to autopsy (Figs. 4-7). Our analysis does not favor the view that all instances of the  $T_N$  contour are due to diffuse pericarditis.

It is obviously important to differentiate these cases from those of pericarditis without infarction, in which inverted T waves in the three limb leads are also found. Other criteria, especially the QRS pattern, the contour of the chest leads, and/or the evolutionary changes together with the clinical history and findings are important in making this differential diagnosis.<sup>36, 37</sup>

In discussing the  $T_N$  pattern we lay claim neither to prior discovery nor to unusual observation. Perusal of the literature reveals that as early as 1925 Willius and Barnes<sup>30</sup> pointed out that 5 of their 9 patients with coronary occlusion showed inverted T waves in all three limb leads and that the same phenomenon could be seen in other isolated instances. All cardiographers have undoubtedly seen such in their own experience. The greater incidence in our series than its general occurrence in the collected literature is perhaps due to our insistence, when feasible, on frequent electrocardiographic records on all recent myocardial infarcts, since many times the  $T_N$  pattern is present only for a short time.

#### SUMMARY AND CONCLUSIONS

1. In sixty cases from the files of the Heart Station in the last ten years there were simultaneously inverted T waves in all three limb leads at some stage in the evolution of the electrocardiogram following acute myocardial infarction. This pattern is called the  $T_N$  pattern to conform with the nomenclature in common use.

2. Seven different mechanisms are presented as being possible factors in the production of this pattern and four further ones are suggested.

3. The importance of realizing that the T waves following acute myocardial infarction may be inverted in both Lead I and Lead III instead of presenting a reciprocal appearance is stressed.

We are indebted to the physicians of the Hospital staff for their kind permission to use their cases in this report; the autopsies were performed by Dr. O. Saphir.

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## MURAL THROMBI IN THE HEART

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IN 1809, Burns<sup>1</sup> differentiated endocardial thrombi from agonal and post-mortem clots and various tumor masses. Since then the morphology of mural thrombi has been well understood, but the mechanism of formation is still in doubt.

Hunter<sup>2</sup> (1794) thought that thrombi consisted of exudate from an infected vessel wall; Cruveilhier<sup>3</sup> (1829) believed the reverse, namely, that the clot came first and the infection second. Andral<sup>4</sup> (1842) postulated a combination of stasis and infection. Virchow<sup>5</sup> (1855) first pointed out that sluggish circulation and changes in the quality of the blood might produce thrombosis without infection, and, in substantiation of this viewpoint, Zahn<sup>6</sup> (1874) produced thrombosis by injuring vessel walls. Various other contributions have gradually led to the modern concept of the formation of thrombi, which stresses physical, chemical, and colloidal changes in the blood, as well as endothelial injury and stasis.

With regard to the etiology of mural thrombi, Harvey and Levine,<sup>7</sup> after studying 111 mural thrombi which occurred in 2,091 consecutive autopsies, decided that myocardial degeneration and auricular fibrillation were most important. Cleland<sup>8</sup> encountered sixty-nine mural thrombi in 3,000 autopsies, and stressed myocardial infarction and cardiac dilatation, with back pressure extending to the auricles. In 46.7 per cent of Meakins and Eakin's<sup>9</sup> cases of coronary thrombosis there were mural thrombi. Blumer<sup>10</sup> concluded that mural thrombi occurred in 50 per cent of cases of infarction. Graef, et al.,<sup>11</sup> found auricular thrombosis in 13 per cent of 178 rheumatic hearts. They concluded that mitral stenosis, congestive heart failure, auricular fibrillation, and localized inflammation favored the formation of auricular thrombosis in rheumatic heart disease.

The material for this study of mural thrombi consists of clinical and pathologic observations on 771 consecutive, adult, autopsied patients in whom heart disease was the chief cause of death. These cases occurred in 6,285 consecutive post-mortem examinations done at the Cleveland City Hospital from January, 1930, to June, 1939, inclusive.

*Distribution of Mural Thrombi by Chambers.*—Of the 771 patients, 265, or 34.4 per cent, had one or more ante-mortem, mural thrombi in the heart, as shown in Table I.

From Table I it is seen that in 170 cases (64.2 per cent) mural thrombi were found in only one chamber of the heart; the chambers involved,

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TABLE I  
DISTRIBUTION OF MURAL THROMBI BY CHAMBERS

LOCATION	NO. OF CASES
Left ventricle alone	85
Right atrium alone	59
Right atrium and left ventricle	24
Right ventricle and left ventricle	24
Right atrium and left atrium	19
Left atrium alone	17
Right atrium, right ventricle, and left ventricle	11
Right ventricle alone	9
All four chambers	4
Right atrium and right ventricle	4
Right atrium, left atrium, and left ventricle	3
Right ventricle, left atrium, and left ventricle	3
Left atrium and left ventricle	2
Right atrium, right ventricle, and left atrium	1
Right ventricle and left atrium	0
Total	265

in decreasing order of frequency, were the left ventricle, the right atrium, the left atrium, and the right ventricle. In seventy-three cases (27.5 per cent) mural thrombi were present in two chambers. Three chambers were involved in eighteen cases (6.8 per cent), and all four chambers in four cases (1.5 per cent).

Further analysis shows that mural thrombi were found in the right and the left sides of the heart as given in Table II.

TABLE II

LOCATION	NO. OF CASES
Left side of the heart only	101
Right side of the heart only	72
Both sides of the heart	89
Total	265

Stated differently, one-third of 771 patients who died of heart disease had mural thrombi in one or more chambers of the heart; one-fourth had thrombi in the left side of the heart; one-fifth had thrombi in the right side of the heart; and one-ninth had mural thrombi in both sides of the heart.

*The Incidence of Mural Thrombi in Various Types of Heart Disease.*—The incidence of mural thrombi varied with the type of heart disease (Table III). Coronary artery disease, with coronary thrombosis and myocardial infarction, was the type of heart disease most likely to be associated with mural thrombi; two out of every three patients had this complication. Coronary artery disease without myocardial infarction and with or without hypertensive heart disease, hypertensive heart disease itself, and rheumatic heart disease were virtually alike, with mural thrombi in about one case in three. Only one of five patients who died of syphilitic heart disease had mural thrombi, and this complication was distinctly uncommon in cor pulmonale and subacute and acute bacterial endocarditis.

*Coronary Artery Disease With Myocardial Infarction, With or Without Associated Hypertensive Heart Disease (133 Cases, in Eighty-nine of Which There Were Mural Thrombi).*—Sixty per cent of the mural thrombi found in this group were located on the endocardial surface at the point of infarction. Evidence pointing to the etiological importance of infarction as a cause of mural thrombi is afforded by the fact that, of eighty-nine patients who had one myocardial infarct, fifty-five, or 61.8 per cent, had mural thrombi, whereas of thirty patients who had two or more infarcts, twenty-six, or 86.7 per cent, had mural thrombi; this is a significant difference.\*

TABLE III  
INCIDENCE OF MURAL THROMBI IN VARIOUS TYPES OF HEART DISEASE

TYPE OF HEART DISEASE	NO. OF CASES	NO. WITH MURAL THROMBI	PER CENT
Coronary artery disease with infarction (with or without hypertensive heart disease) <sup>1</sup>	133	89	66.9
Coronary artery disease without infarction (with or without hypertensive heart disease) <sup>1</sup>	94	33	35.1
Hypertensive heart disease	147	46	31.3
Rheumatic heart disease	116	37	31.9
Syphilitic heart disease	67	13	19.4
Cor pulmonale	50	3	6.0
Subacute bacterial endocarditis	30	1	3.3
Hypertensive heart disease complicated by various types of heart disease	15	7	46.6
Hypertensive heart disease complicated by rheumatic heart disease	13	6	46.2
Acute bacterial endocarditis	13	0	0.0
Coronary artery disease without infarction, complicated by various types of heart disease	10	4	40.0
Aortic stenosis	8	2	25.0
Thyroid heart disease	8	0	0.0
Obliterative pericarditis	7	0	0.0
Tuberculous pericarditis	7	0	0.0
Coronary artery disease with infarction, complicated by various types of heart disease	5	2	40.0
Undiagnosed	34	17	50.0
Miscellaneous	14	5	35.7
Total	771	265	34.4

<sup>1</sup>Whether or not there was associated hypertensive heart disease made no appreciable difference.

The locations of the mural thrombi in this group are given in Table IV. The predominant frequency of thrombi in the left ventricle, the portion of the heart most often affected by infarction, is apparent.

There was no significant association between the occurrence of mural thrombi in this group and such factors as sex, age by decades, the number of attacks of congestive failure, the presence or absence of auricular fibrillation, and the degree of hypertrophy of the heart.

\*In this article, the term "significant" refers to a difference which could be produced by chance in less than 5 per cent of trials, as demonstrated by application of the chi square test; "highly significant" refers to a difference so great that it could be produced by chance in less than 1 per cent of trials, again as demonstrated by application of the chi square test.

TABLE IV

LOCATION	NO. OF CASES
Left ventricle alone	46
Left ventricle and right ventricle	13
Left ventricle, right ventricle, and right atrium	8
Left ventricle and right atrium	7
Right atrium alone	6
Left ventricle, right ventricle, and left atrium	3
Right atrium and left atrium	2
Right ventricle alone	1
Right ventricle and right atrium	1
Left ventricle and left atrium	1
All four chambers	1
Total	89

*Coronary Artery Disease Without Infarction, With or Without Associated Hypertensive Heart Disease (Ninety-four Cases, in Thirty-three of Which There Were Mural Thrombi).*—The locations of the mural thrombi in this group are given in Table V.

TABLE V

LOCATION	NO. OF CASES
Left ventricle alone	13
Left ventricle and right atrium	6
Right atrium alone	4
Right atrium and left atrium	3
Right ventricle and left ventricle	3
Right atrium, right ventricle, and left ventricle	2
Left atrium alone	1
Right atrium, left atrium, and left ventricle	1
Total	33

No association could be demonstrated between the occurrence of thrombi and such features as sex, age, the number of attacks of congestive failure, the presence or absence of auricular fibrillation, and the degree of hypertrophy of the heart.

*Uncomplicated Hypertensive Heart Disease (147 Cases, in Forty-six of Which There Were Mural Thrombi).*—The distribution of the thrombi is given in Table VI.

TABLE VI

LOCATION	NO. OF CASES
Left ventricle alone	11
Right atrium alone	10
Right atrium and left ventricle	6
Right atrium and left atrium	5
Right ventricle and left ventricle	5
Right ventricle alone	3
Right atrium and right ventricle	2
All four chambers	2
Left atrium alone	1
Right atrium, left atrium, and left ventricle	1
Total	65

There was a significant association between the occurrence of mural thrombi and age, as shown in Table VII.





TABLE IX

DISTRIBUTION OF MURAL THROMBI ACCORDING TO AGE IN CASES OF RHEUMATIC HEART DISEASE

AGE GROUP	NO. OF CASES	PATIENTS WITH MURAL THROMBI	PER CENT
10-39	55	10	18
40-49	23	9	39
50-79	38	18	47.4

ence or absence of auricular fibrillation, for 68.4 per cent of these older patients had auricular fibrillation, whereas fibrillation occurred in only 39.6 per cent of the younger patients; this difference is highly significant. This increasing incidence of mural thrombi in the older patients with rheumatic heart disease is exactly the opposite of the situation in hypertensive heart disease.

Although thrombi occurred 10 per cent more often in cases in which there had been two or more attacks of congestive failure than in those in which there had been only one, this difference was not significant statistically. No association between mural thrombi and sex or degree of hypertrophy of the heart was demonstrable.

*Syphilitic Heart Disease (Sixty-seven Cases, in Thirteen of Which There Were Mural Thrombi).*—The distribution of the thrombi is given in Table X.

TABLE X

LOCATION	NO. OF CASES
Right atrium alone	9
Right ventricle alone	1
Left atrium alone	1
Left ventricle alone	1
Right atrium and right ventricle	1
Total	13

There was no association between the occurrence of thrombi and sex, age, number of attacks of congestive failure, cardiac mechanism, or degree of cardiac hypertrophy.

## SUMMARY

Of 771 consecutive, adult, autopsied patients who died of heart disease, 265, or 34.4 per cent, had one or more mural thrombi. Coronary artery disease, with myocardial infarction, was the type of heart disease most often associated with mural thrombi; in two-thirds of these cases this complication was present. Mural thrombi were associated with coronary artery disease without myocardial infarction, hypertensive heart disease, and rheumatic heart disease, in one-third of the cases; they were present in one-fifth of the cases of syphilitic heart disease, but were uncommonly found in cases of cor pulmonale and bacterial endocarditis.

Most of the mural thrombi in cases of coronary artery disease with myocardial infarction were caused by the infarction itself and were located in the left ventricle.

In hypertensive heart disease, about 60 per cent of the patients below 40 years of age had mural thrombi, whereas only 20 per cent of those who were 60 years of age or older had this complication. This significant difference is unexplained.

In rheumatic heart disease, mural thrombi occurred two and a half times as often in patients with auricular fibrillation as in those with normal mechanism; this is highly significant. The thrombi were present in the right atrium and/or the left atrium in 86.5 per cent of the cases, and this is probably another indication of the importance of auricular fibrillation. There was a highly significant preponderance of mural thrombi in older patients, presumably because of the greater frequency of auricular fibrillation in this group.

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#### DISCUSSION

DR. S. A. LEVINE, Boston.—One unanswered question that is of great importance to us practically is, when do the thrombi form? We know pretty clearly when they form in the left ventricle after coronary occlusion. I think there is sufficient evidence that thrombosis of the left ventricle follows, rather than precedes, the infarction. Thrombi in the auricles were the immediate cause of death in 20 per cent of all cases of rheumatic heart disease at the Brigham Hospital. It is a big problem, but we do not know when the thrombus forms. Even the role that fibrillation plays is not altogether clear. We found a very high incidence of mural thrombosis in the auricles in cases of mitral stenosis with normal rhythm, and I suggest that Dr. Garvin would find that the average age at death of the patients with normal rhythm was a good deal less than that of the patients with auricular fibrillation. Therefore, those with fibrillation had a few years longer to produce mural thrombosis. We must admit that fibrillation, per se, must be play-

ing a role because of the rare experience, and it is a rare one, but one that we should bear in mind, namely, that a thrombus can form in the auricles in cases of so-called normal persons with fibrillation.

I had the experience of seeing such a patient; he had no hypertension or coronary disease, but had fibrillation without symptoms except palpitation. Later he developed a left mural thrombus.

I think we still need to reconsider the exact role that auricular fibrillation plays in cases of mitral stenosis and what part the time element plays. The longer a person with heart disease lives, the more opportunity there is to have a mural thrombus.

It is interesting that thrombi were very rare in cases of subacute bacterial endocarditis. One would have expected, as a matter of chance, that more thrombi would have been found; this makes one think that these patients who have subacute bacterial endocarditis are running an entirely different clinical course, and that their reactions differ from those of patients with other kinds of rheumatic hearts. They have less reactivation of the rheumatic infection. If we knew when the thrombus is due to form or might be formed, we would be challenged to stop it or dissolve it. Nowadays, with the introduction of heparin, we must be thinking about the possibility of preventing mural thrombosis in heart disease because it is not only found at autopsy, but is an important cause of death in an appreciable number of patients.

It is interesting that thrombi occurred in so-called hypertensive heart disease. That term is commonly used in diagnosis, but I do not think it explains the disease. I see no reason why, in real hypertensive heart disease, there should be thrombosis, and the occurrence of this thrombosis in hypertensive heart disease in the young, that is, from 10 to 39, means to me that something other than hypertensive heart disease was the cause of death, and that the diagnosis of hypertensive heart disease was not correct.

DR. ROBERT L. LEVY, New York.—I should like to ask two questions. First, was the incidence of mural thrombi related in any way to the presence or absence of congestive failure? Second, was there any relationship, in the various groups, between the presence of mural thrombi and the occurrence of embolism?

DR. CURTIS F. GARVIN, Cleveland.—In regard to Dr. Levy's question, virtually all of these patients had heart failure; they died of heart disease. The only exceptions of any consequence would be in some of the cases of coronary thrombosis and subacute bacterial endocarditis. Second, I did not investigate embolism. I presume the fact that there was heart failure accounted for the occurrence of mural thrombi in hypertensive heart disease.

## THERAPEUTIC VENOUS OCCLUSION

ITS EFFECT ON THE ARTERIAL INFLOW TO AN EXTREMITY, AS MEASURED  
BY MEANS OF THE REIN THERMOSTROMUHR\*

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**T**HERAPEUTIC venous occlusion is a subject which has been under discussion for the last thirty years. The question of what effect it has upon the arterial inflow to an extremity has never been satisfactorily answered. In acute arterial insufficiency, the evidence from a clinical point of view indicates that there is an increase in the arterial blood flow following venous occlusion. In chronic obliterative vascular disease, more evidence is accumulating to show that the blood flow may be increased by the same method.

The following brief review of the literature is of interest in a reconsideration of this problem. Oppel,<sup>1</sup> in 1913, reported beneficial results following ligation of the femoral vein in six cases of arteriosclerotic obliterative disease. Lilienthal,<sup>2</sup> in 1914, and Ginsburg,<sup>3</sup> in 1917, advocated femoral vein ligation in thromboangiitis obliterans. Morton and Pearse,<sup>4</sup> in 1928, and Van Gorder,<sup>5</sup> in 1929, noted favorable results from therapeutic venous occlusion in obliterative vascular disease. Although there was considerable evidence that the circulation could be improved by high venous ligation, the results fell short of what had been anticipated, so that the operation has fallen into discard. Collens and Wilensky,<sup>6, 21</sup> in 1936, introduced a nonoperative method of producing intermittent venous occlusion; it was obtained by applying a pneumatic tourniquet to the proximal portion of an extremity. The tourniquet is connected to an electrically controlled pump, which inflates it at regular intervals and automatically releases the pressure. This type of venous occlusion has proved to be of value, in both acute and chronic obliterative vascular disease, in the development of a collateral circulation to an extremity with deficient arterial supply.

Following acute occlusion of a major artery to an extremity, there is practically universal agreement that ligation of the concomitant vein is beneficial. Makins,<sup>7</sup> reporting on his experiences in the British Army Medical Service during the world war of 1914-1918, stressed the importance of ligating the concomitant vein when it is necessary to ligate a major artery to a limb. He is reported to have recognized this first during the Boer war, 1899-1901, and it was largely through his studies

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that the Interallied Congress of Surgeons, in 1917, accepted the principle of simultaneous ligation of the vein. He reported 172 cases of injury to the arteries of the extremity, in which the artery alone was ligated in 101, with gangrene in twenty-nine cases, or 28 per cent, and seventy-one cases in which both artery and vein were ligated, with gangrene in fourteen, or 19.7 per cent. Tuffier,<sup>8</sup> in 1917, reported that ligation of the popliteal artery alone in twenty-four cases gave favorable results in fourteen, or 58.33 per cent, and led to gangrene in ten, or 41.66 per cent, whereas simultaneous ligation of the artery and vein in twenty-eight cases produced favorable results in twenty-two, or 78.6 per cent, and caused gangrene in only six, or 21.4 per cent. Sehrt,<sup>9</sup> in 1916, reported similar results when the artery alone was ligated; gangrene occurred in 20.4 per cent of the cases, whereas it was seen in only 9 per cent when both the artery and vein were tied. Heidrick,<sup>10</sup> in 1921, reported an incidence of gangrene of 15.4 per cent in 995 cases after ligation of a large artery, whereas the incidence was only 8.5 per cent in 198 cases in which both the artery and vein were ligated. Holman,<sup>11</sup> in 1927, and Pemberton and McCaughan,<sup>12</sup> in 1932, recommended simultaneous vein ligation.

Experimental investigations of this improvement in the circulation after venous occlusion have not given uniform results. Brooks and Martin,<sup>13</sup> in 1923, confirmed the clinical results by experiments carried out on a series of rabbits. They found that, when the common iliac or external iliac arteries were ligated, gangrene developed in 71.5 per cent of the animals, whereas, in a second series, in which there was added to this procedure ligation of the common iliac vein, the incidence of gangrene was only 33.3 per cent. These results were corroborated by Holman,<sup>11</sup> in 1927. He found that, when the common iliac artery and inferior vena cava were ligated simultaneously in eighteen rabbits, only two developed gangrene. In ten other rabbits in which the common iliac and external iliac arteries and the inferior vena cava were simultaneously ligated, there were no cases of gangrene, so that, of twenty-eight animals, gangrene developed in only 7.1 per cent.

Attempts have been made to explain the improvement of the circulation which results from simultaneous vein ligation in both clinical and experimental acute arterial occlusion. Studies have been carried out by several investigators to ascertain the effect of venous occlusion on the arterial flow of the extremity. Brooks and Martin,<sup>13</sup> in 1923, studied the effects of simultaneous ligation of the vein and artery of a dog's leg, under anesthesia, by measuring the temperature of the tissues distal to the ligature. In these experiments they found a decrease distal to the ligature after ligation of the concomitant vein and acute arterial occlusion, and from this they assumed that the volume flow had decreased. The most recent experimental work with reference to this subject was reported by Montgomery,<sup>14</sup> in 1932. It supports Brooks and Martin's studies on tissue temperature. He used a direct, continu-

ous volume flow apparatus, which was a modification of the Ludwig stromuhr and Stolinkow's double inlet-outlet apparatus, to measure the arterial inflow before and after venous ligation. He concluded that ligation of the concomitant vein after ligation of the superficial femoral artery resulted in no change, or a slight decrease, in the volume flow in the iliac artery, and a more marked decrease when the venous return was obstructed proximal to the site of arterial occlusion. Halsted<sup>15</sup> expressed the opinion purely from theoretical grounds that obstruction of the venous return may disturb the development of a collateral circulation following acute arterial occlusion, whereas La Roque<sup>16</sup> felt that therapeutic vein ligation favored the development of collateral vessels.

Holman,<sup>11</sup> in 1927, and Theis,<sup>17</sup> in 1928, reported an increase in the volume flow of blood after concomitant venous obstruction. Their method of determining the blood flow was to cannulate the artery distal to the point of arterial obstruction and measure the amount of blood which flowed from the cannula over a given period of time, before and after venous ligation. Both of these investigators found that the amount of blood flowing from the cannula was increased after venous obstruction. This method, however, was open to considerable criticism, as it was argued that it merely measured the collateral arterial blood flow, which could more readily pass out through the open artery than it could by way of the venous collateral channels after the main vein had been obstructed. Pearse,<sup>18</sup> in 1927, and Spurrell,<sup>19</sup> in 1930, studied the arterial tree in experimental animals after ligation of the main artery to an extremity, both with and without simultaneous venous ligation. They found that, in the former, the collateral arterial blood supply was developed to a much greater extent than in the latter.

Lewis and Grant,<sup>20</sup> who studied the reactive hyperemia which results from venous congestion in unanesthetized human subjects, made a very important observation. Their method of measuring blood flow to the extremity was by means of venous obstruction, using a plethysmograph to measure the change in size of the extremity. They noted that their plethysmographic tracings showed, during the period of venous congestion, a marked increase in the amplitude of the arterial pulsations. They state: "At the end of ten or fifteen minutes, the increased amplitude (of the arterial pulsations) is usually maximal and is then unmistakable. This increase in the size of the volume pulse forms a first suggestion that *venous engorgement causes dilatation of the vessels on the arterial side.*"\* Collens and Wilensky,<sup>21</sup> in 1936, noted this observation of Lewis and Grant, but nevertheless considered that the increase in arterial inflow *following* the release of venous occlusion was of more significance. From this review of the literature it is clear that there is still a controversy as to whether therapeutic venous occlusion does or does not increase the arterial inflow to an extremity.

\*Authors' (Lewis and Grant) italics.

The purpose of this paper is to present further evidence which was obtained in a series of experiments on dogs. A thermostromuhr method which has been perfected in the Surgical Laboratories of the Harvard Medical School at the Massachusetts General Hospital was used for measuring blood flow. By means of this method, it is possible to measure accurately the minute volume flow of blood in an artery or vein without disturbing the continuity of the blood vessel; this gives it an advantage over other methods. The principle of the thermostromuhr is similar to that of the one originally described by Rein,<sup>22</sup> and later by Herrick and Baldes.<sup>23</sup>

#### EXPERIMENTAL STUDIES

The following is a short description of the thermostromuhr method of measuring the blood flow. The blood is heated at a given point by means of a radio frequency current which is passed through the blood vessel between two platinum electrodes on opposite sides of the vessel. The electrodes are placed equidistant between two thermojunctions, made of copper and constantan wire, that are connected with a galvanometer (Fig. 1). These are joined in series and are known as a differential thermocouple. The platinum electrodes and the thermojunctions are imbedded in a specially constructed bakelite block, as it is important that the radio frequency heating current be completely insulated from the thermocouple circuit. Rubber-covered, insulated wires, to be referred to as leads,\* carry the heating current to the electrodes, and similar ones carry the direct current from the thermocouple to a galvanometer. With a given amount of heating current, the galvanometer deflection varies inversely with the volume flow of blood.

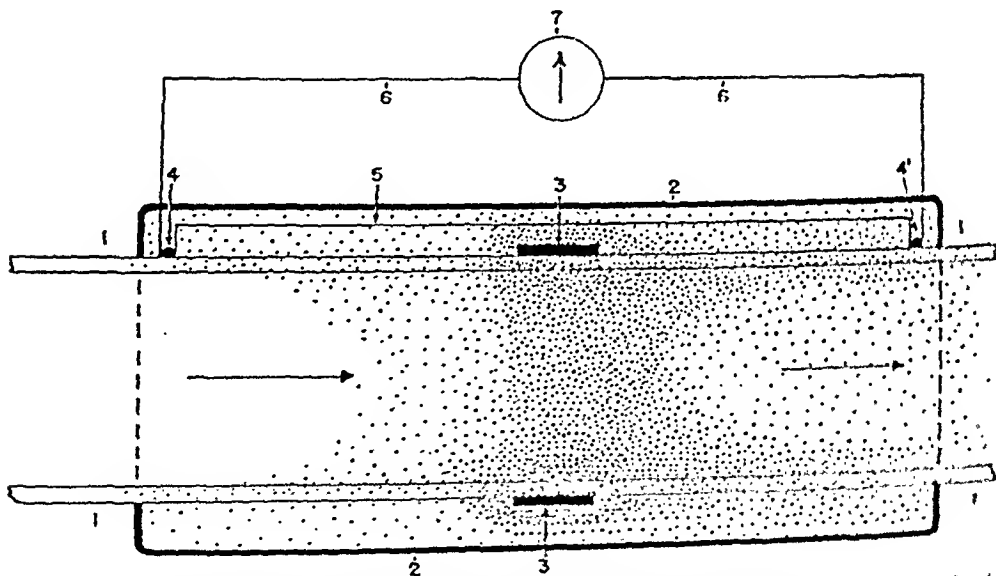


Fig. 1.—A schematic diagram of the application of a blood flow unit to a blood vessel. 1, Blood vessel wall; 2, blood flow unit; 3, platinum electrodes; 4, 4', thermojunctions; 5, constantan wire; 6, copper leads; 7, galvanometer.

The bakelite block in which these wires and electrodes are imbedded contains a groove into which the blood vessel fits (Fig. 2). It is necessary that one have a very tight fit, so that the vessel wall is in apposition with the electrodes and the side of the bakelite block where the thermocouples are imbedded. For this reason

\*Acknowledgment is made to the Simplex Wire & Cable Co., Cambridge, Mass., for their cooperation and aid in the construction of these leads, which are specially constructed, rubber-insulated, multiple-strand, copper-tinsel wires.

it is necessary to have a fairly large number of these units, in order to be sure of obtaining a proper fit; otherwise, erroneous readings are obtained. The proper construction of these units is one of the prime requisites for the successful operation of this method of measuring blood flow. The blood flow studies were carried out on dogs which weighed between 15 and 25 kg. They were anesthetized by the intravenous injection of a 10 per cent solution of sodium amytal. The initial dosage was 50 to 60 mg. per kg. of body weight. It was given in one of the forepaw veins, in order to keep the venous system of the hind leg intact for experimental studies. At varying times during the experiment it was necessary to give additional sodium amytal in 50- to 100-milligram doses intravenously. In the first few experiments the studies were made on the right femoral artery and vein, but in the later

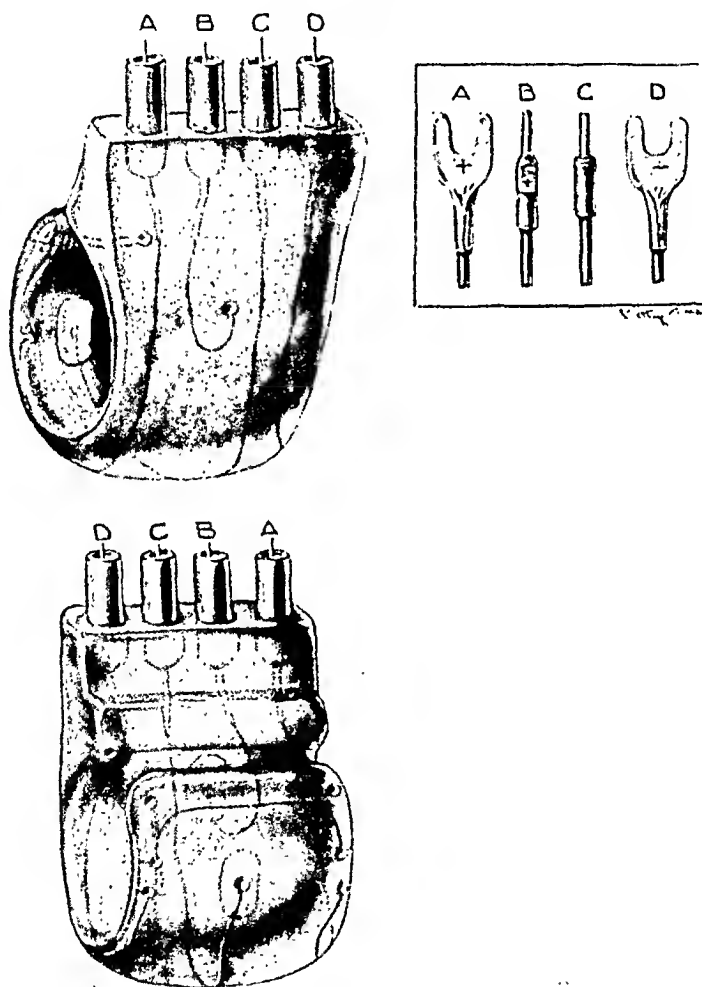


Fig. 2.—A complete blood flow unit, showing the front and back views. A and D, Galvanometer leads; B and C, radio frequency leads. The inset shows the terminals on the leads. (These units are made in the Surgical Laboratories of the Harvard Medical School at the Massachusetts General Hospital.)

experiments the iliac artery and vein, usually on the right side, were used. The latter vessels were exposed by an extraperitoneal approach, as it was found that the animals withstood the experiments much better if the abdominal cavity was not opened. In some cases the inferior vena cava and the common iliac, external iliac, and femoral veins were also dissected out, in order to test the effect on the arterial flow of occlusion of these different veins. Arterial blood pressure was



measured by cannulating one of the carotid arteries. The venous pressure in the extremity which was being studied was measured by cannulating a vein in the lower part of the leg, usually one of the superficial ones. Clotting in this system was prevented by connecting the cannula with a reservoir of saline which contained heparin. In this way it was found unnecessary to heparinize the animal completely. In order to place one of the blood flow units on a vessel, it is necessary to dissect it completely free from the tissues about it for a distance of about 2 cm. Great care was taken not to traumatize the artery while dissecting it free, for even the slightest trauma would throw it into marked vasoconstriction. At the same time, it was extremely important that the wall of the vessel be cleaned thoroughly of excess tissue. Occlusion of the veins was produced by passing silk ligatures around them. Both ends of the ligature were then passed out through a glass tube of small caliber. The tube was inserted through a small stab wound in the skin, and pushed directly through the muscles and fascia, so that the inner end of it was in close approximation to the vein. The glass tube was then fixed by means of clamps to prevent it from moving when traction was exerted on the silk thread. In this manner it was possible to impinge the vein against the inner end of the tubing, and thus produce complete occlusion of the vessel. Releasing the ligature, in most instances, if the glass tubing had been correctly placed, would relieve the venous obstruction.

After careful dissection of the femoral or iliac artery, the vessel was measured and the correct unit applied to it. The unit was fixed in place by suturing it to the adjacent muscles; this was done in order to prevent displacement in case there was undue traction on the leads. After it was ascertained that the venous ligatures and the unit were properly placed, the wound was closed in layers. In one animal the blood flow unit was placed on the iliac artery, under aseptic precautions. The effect on the arterial blood flow of venous congestion produced by a pneumatic tourniquet on the thigh and digital compression of the femoral artery were studied without anesthesia. These experiments were carried out the day after the operation (Fig. 9). Experiments were done on ten other dogs, under sodium amytal anesthesia. After the completion of an experiment, the animal was sacrificed by bleeding it from the carotid artery. The blood was collected and defibrinated.

The vessel and the blood flow unit were removed intact. They were placed in a constant temperature calibrating apparatus (Fig. 3), surrounded by blood from the same animal. The blood vessel was connected with a circulating system containing the defibrinated blood. By means of this apparatus, it was possible to maintain the blood pressure which the animal had had during the experiment, and also to vary the volume flow per minute through the vessels. The galvanometer deflection was recorded for each rate of blood flow. In this way a calibration curve was obtained, and, by means of it, it was possible to ascertain the actual amount of blood flow through the iliac artery in the dog by referring to the records taken at the time of the experiment. The different experiments carried out on this group of animals have been divided into six series.

## RESULTS

*Series 1. The Effect of Venous Occlusion in the Ipsilateral Limb on the Normal Arterial Blood Flow to an Extremity.*—The blood flow through a dog's femoral artery was measured before, during, and after occlusion of the ipsilateral femoral vein for periods varying from two to thirty-four minutes. The femoral artery and vein on the right side were dissected free through a small skin incision. A blood flow unit of the proper size was placed on the femoral artery, and a silk ligature was

placed around the femoral vein, as previously described. A record of the blood flow, as measured by the galvanometer deflection, was made on photographie paper. The blood flow before the occlusion was usually found to be very constant, providing the animal was not too lightly anesthetized. In some cases, if the dog was shivering even though anesthetized, there were marked fluctuations in the blood flow. A supplementary injection of sodium amytal would stop the shivering, and then the blood flow would immediately become stabilized. As a record of the normal flow was being taken, sufficient traction was exerted on the suture around the femoral vein to occlude it completely. Within a very few seconds there was a very rapid and marked increase in arterial blood flow (Fig. 4). This was constant, regardless of whether the measurements were on the femoral or iliae artery. The flow usually reached a maximum within one minute, where it remained a short time. It then

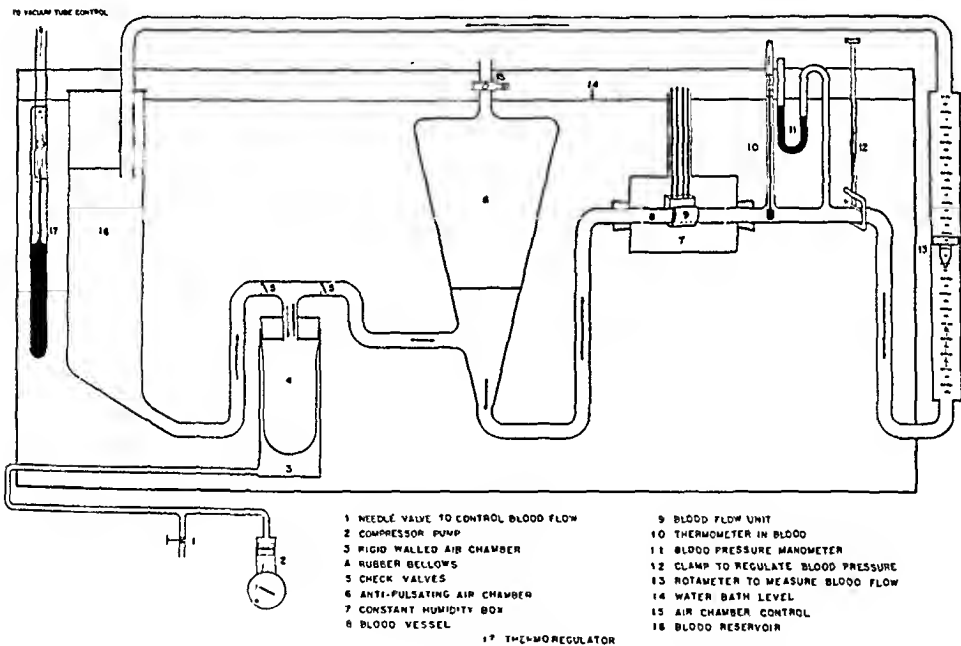


Fig. 3.—A schematic diagram of the constant temperature calibrating apparatus.

decreased gradually to a constant level that was always 30 to 50 per cent above normal. In one case, occlusion of the femoral vein was carried out for a period of thirty-four minutes (Fig. 4). In most cases, on release of the venous occlusion there was a very rapid and sudden decrease in the arterial blood flow, well below the normal level. This effect was only transitory, lasting ten to thirty seconds. Then the flow returned to a level between the maximum and the normal (Fig. 4). In the animal in which the occlusion lasted thirty-four minutes, the blood flow had returned to the normal level within one to two minutes after the release of the femoral vein, and in five minutes it was found to be less than before the occlusion was produced. In the record shown

(Fig. 4), the flow during three-minute occlusion increased from approximately 100 c.c. per minute to 230 c.c. a minute within the first minute of occlusion; after this there was a gradual decline in the volume flow to about 140 c.c. a minute at the end of the three-minute period. In the experiment in which the occlusion lasted thirty-four minutes, the initial flow was around 110 c.c. a minute; after the occlusion this increased to approximately 155 c.c. a minute, then fell to about 145 c.c. a minute, where it became stabilized and remained until the termination of the venous occlusion, as the tracing and graph show (Fig. 4).

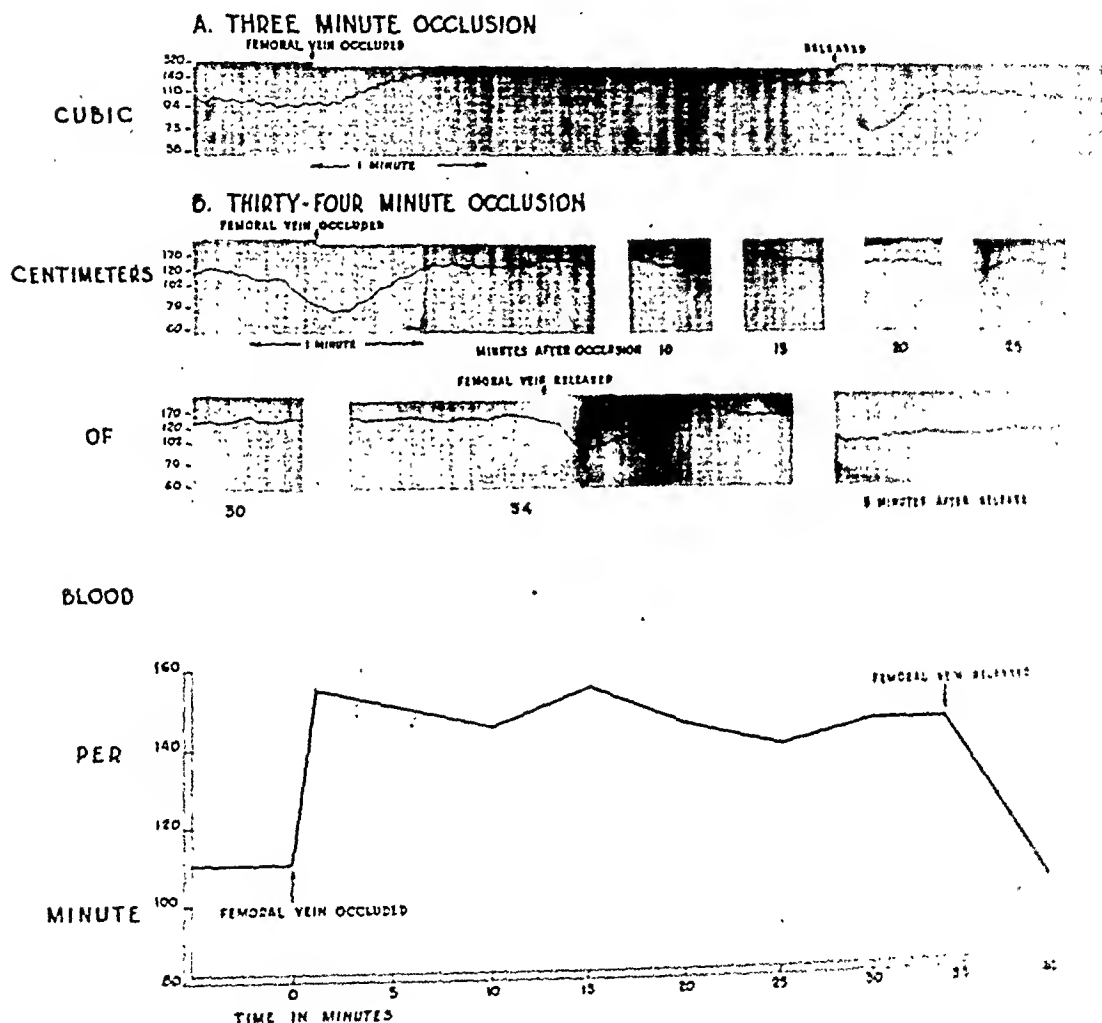


Fig. 4.—The effect of venous occlusion in the ipsilateral limb on the normal arterial blood flow to an extremity (sodium amytal anesthesia). Note the rapid increase in the femoral artery blood flow after occlusion of the femoral vein in the three-minute occlusion record, namely from 100 c.c. per minute to 230 c.c. per minute. In the thirty-four-minute record, the increase is from 110 c.c. per minute to 155 c.c. per minute. It is also to be noted that the blood flow persisted at 145 c.c. per minute until the femoral vein was released. This shows that the increase in arterial blood flow is concomitant with the venous occlusion.

From this series of experiments it was clear that obstruction of the ipsilateral femoral vein in the presence of a normal femoral arterial blood flow increased the blood flow through the femoral artery for

a short period by more than 100 per cent, and that, over a prolonged period of time (one-half hour), a 33 per cent increase persisted.

*Series 2. The Effect of Venous Occlusion in the Contralateral Limb on the Normal Arterial Blood Flow to an Extremity.*—It was thought important to investigate whether this increase in arterial inflow was a local effect in the extremity in which the occlusion was produced, or whether it was a generalized effect, caused perhaps by a humoral or a nervous mechanism. Therefore, the blood flow through a dog's femoral artery was measured before, during, and after occlusion of the contralateral femoral vein for two- and three-minute periods. The results of these experiments are shown in Fig. 5. In one case the arterial blood flow was approximately 60 c.e. before, during, and after venous occlusion. In the other it remained around 110 c.e. per minute. Comparison of the latter record with those in Fig. 4 shows very well the different effect on the arterial inflow which is produced by occlusion of the ipsi- and the contralateral femoral veins in the same animal. It seemed from these experiments that the increased arterial inflow produced by venous occlusion was localized to the extremity in which the venous occlusion was produced, and that it was not a generalized effect.

*Series 3. The Effect of Venous Occlusion on the Iliac Artery Blood Flow in the Presence of Acute Arterial Insufficiency.*—In this group of experiments the effect of occlusion of the ipsilateral common iliac vein on the blood flow through the iliac artery was measured after occlusion of the femoral artery. The blood flow unit was placed on the iliac artery in the usual manner, and a suture was passed around the common iliac vein proximal to the level of the unit. A similar suture was placed on the femoral artery below the inguinal ligament. The locations of these various sites are shown in Fig. 6. Examination of the blood flow records from one of these experiments (Fig. 7) shows that there was a marked diminution in the arterial inflow through the iliac artery after occlusion of the femoral artery; it declined from approximately 450 c.e. a minute to about 60 c.e. a minute. Then, after occlusion of the iliac vein, there was a marked increase in the blood flow, reaching about 140 to 150 c.e. a minute. It should be noted that the increase in the arterial flow after venous occlusion in this experiment occurred much less rapidly than when the entire arterial blood supply was intact. In the latter instance, the arterial inflow reached a maximum within one-half to one minute, whereas, in this experiment, the blood flow after venous occlusion required two and one-half minutes to reach a maximum. It seems reasonable that such should be the case, for there is less blood entering the limb, and, as a result, the venous reservoirs of the leg are filled much more slowly than when the blood supply is intact. The significance of these observations will be discussed later. After release of the iliac vein, the arterial blood flow returned to the level where it had been previous to its occlusion. Release of the femoral

artery resulted in a blood flow which was slightly greater for a few minutes than the preocclusion figure (evidence of a slight reactive hyperemia); it then returned to the previous level. The blood pressure throughout this experiment (Fig. 7) showed essentially no change.

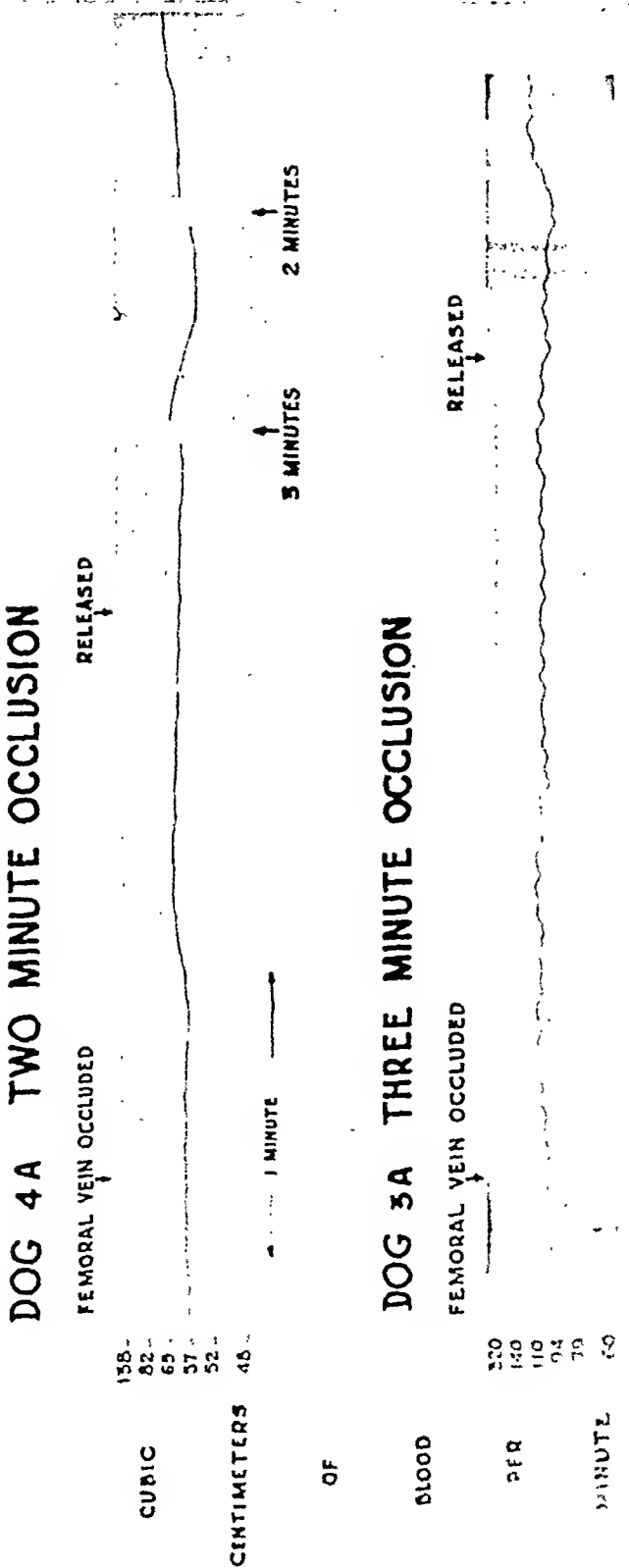


Fig. 5.—The effect of venous occlusion in the contralateral limb on the normal arterial blood flow to an extremely (sodium amytal anesthetized). Note that there is practically no change in blood flow after the venous occlusion, nor upon its release, in either of these records. Compare the three-minute occlusion in dog 3A in this figure with the three-minute occlusion in Fig. 4, as these records were taken on the same animal. Note the marked difference in the effect on the arterial blood flow.

*Series 4. The Comparative Effect on the Iliac Artery Blood Flow Produced by Occlusion of the Femoral and External and Common Iliac Veins.*—The animals in this experiment were prepared like the others, except that, in addition to placing the blood flow unit on the iliac artery, silk threads were placed around the common iliac vein, the external iliac vein, and the femoral vein, so that each one of these vessels could be occluded separately. The venous pressure in the lower part of the leg was also recorded. The effect of occlusion of the femoral, then the external, and finally the common, iliac vein is shown in Fig. 8A. It is to be noted that the iliac artery blood flow increased from approximately 115 e.c per minute to about 145 e.c. per minute;

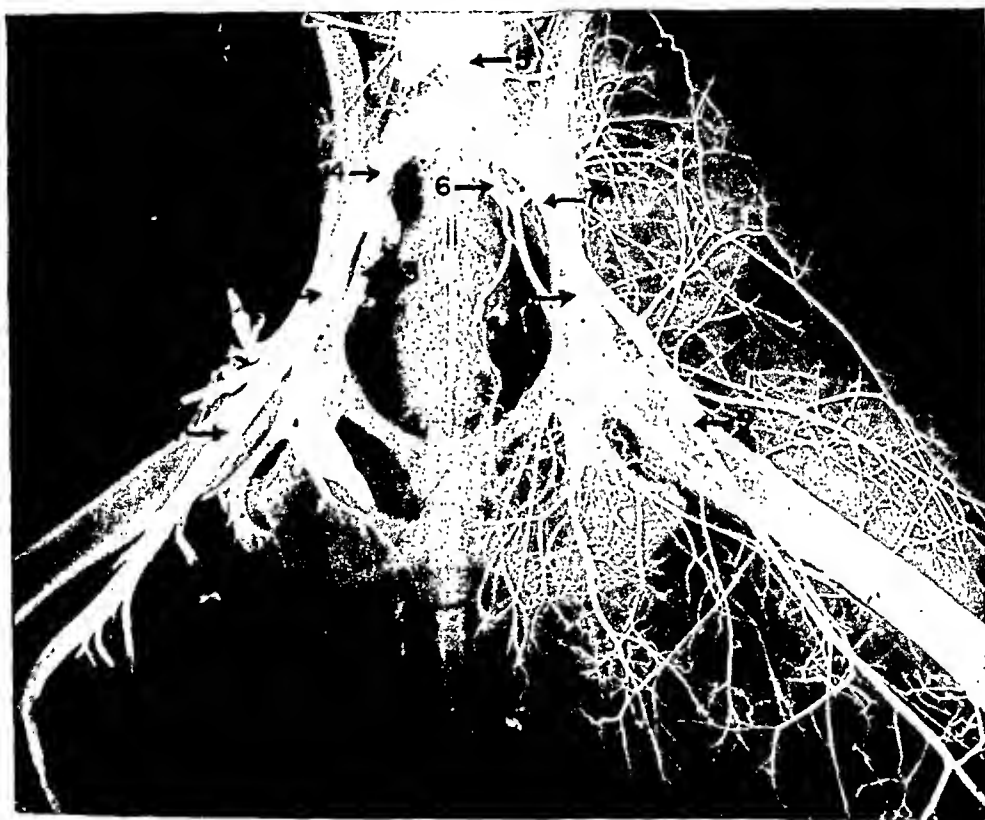


Fig. 6.—The arterial and venous system of a dog's hind leg, injected with barium sulfate. 1, Femoral vein, 2, external iliac vein; 3, internal iliac vein; 4, common iliac vein; 5, aorta; 6, hypogastric artery; 7, iliac artery; 8, deep femoral artery; 9, femoral artery (below the inguinal ligament).

coincidentally, there was a rise in the venous pressure from 5 to 22 mm. of mercury. The external iliac vein was then occluded after one and one-half minutes, without releasing the femoral vein. There was a further increase in the blood flow to approximately 210 to 215 e.c. a minute, and also an elevation in the venous pressure to 25 mm. With both of these veins shut off, the common iliac vein was finally occluded for a minute and a half. This produced very little, if any, change in the blood flow through the iliac artery or in the venous pressure level. The failure of the latter to increase is thought to explain

the lack of an increase in blood flow following occlusion of the common iliac vein. From this experiment it appears that the increase in arterial inflow which is produced by venous occlusion bears a direct relationship to the level of the venous pressure. This fact is further borne out in the following experiment.

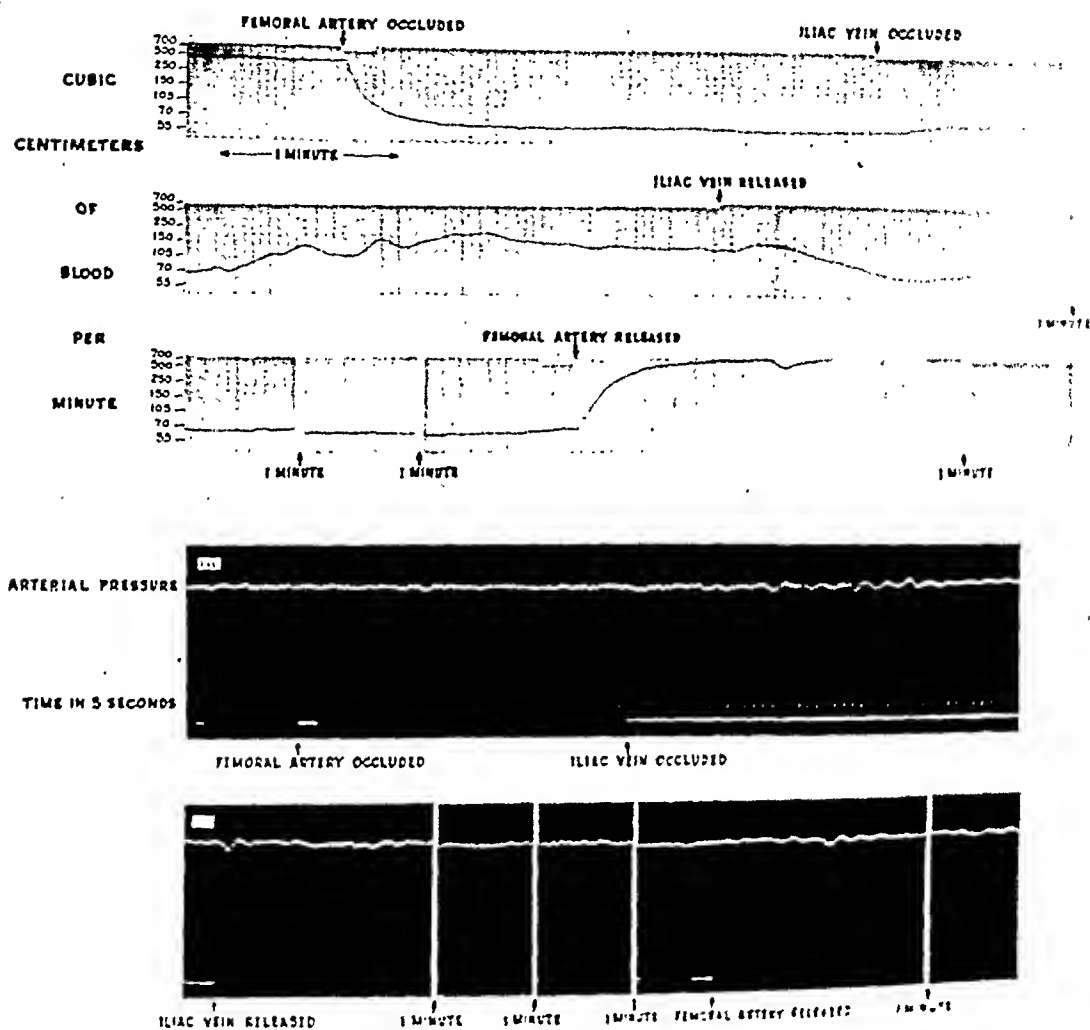


Fig. 7.—The effect of venous occlusion on the iliac artery blood flow in the presence of acute arterial insufficiency (sodium amytal anesthesia). After occlusion of the femoral artery, note the decrease in arterial blood flow from 450 c.c. a minute to 60 c.c. a minute, and the increase in blood flow to 110 or 150 c.c. a minute after occlusion of the iliac vein. It will be seen that this increase paralleled as far as the occlusion was present, and that, after the release of the iliac vein, the flow returned to the preocclusion level. This experiment had no effect on the blood pressure of the animal.

*Series 5. The Effect on the Iliac Artery Blood Flow of Increasing Venous Pressure by Applying a Pneumatic Tourniquet to the Thigh.*—These experiments were carried out on the same animals which were used in Series 4. It was therefore possible to compare the relative effects of occluding the main veins of the extremity with those produced by a tourniquet placed around the upper part of the thigh. It seems probable there should be a difference, for occlusion of the vessels

themselves leaves collateral venous channels open, through which blood may return to the heart, whereas occlusion by means of a tourniquet must affect all of the venous channels. In the latter instance, blood gets back to the heart only when the pressure in the venous channels becomes sufficiently high to equalize and overcome that of the tourniquet.

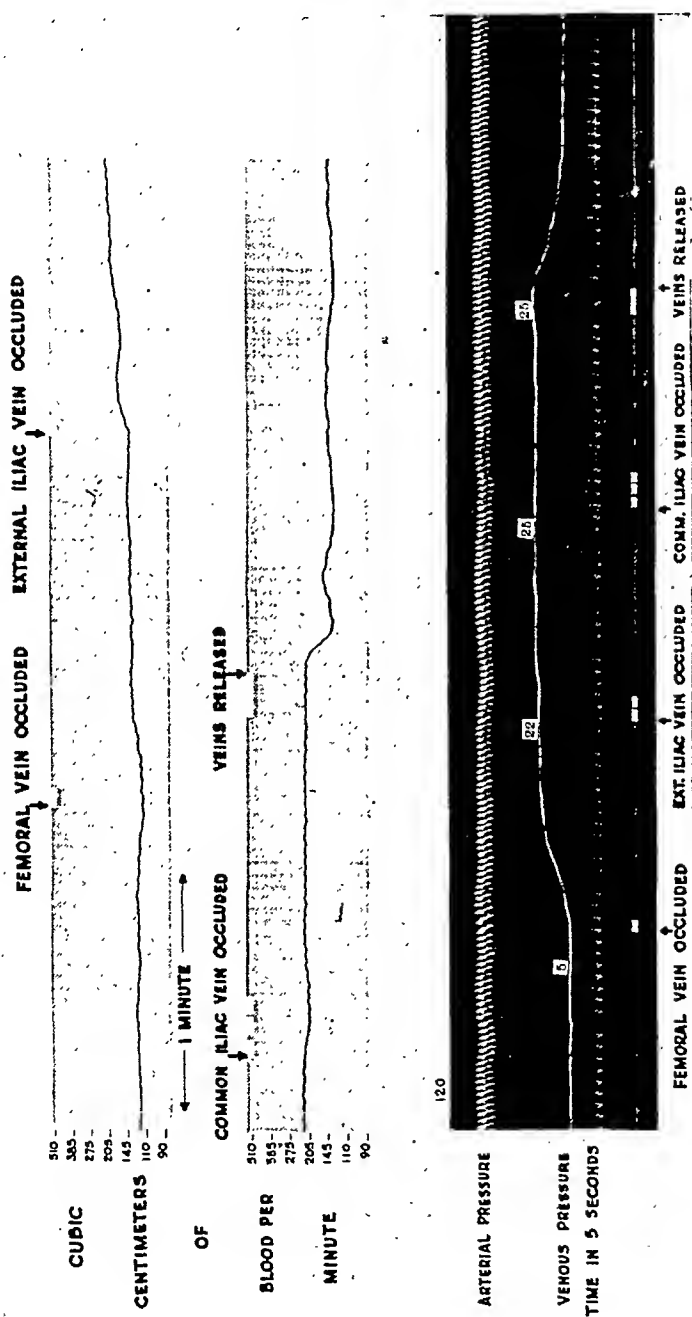


Fig. 8A.—The comparative effect on the iliac artery blood flow produced by occlusion of the femoral, external iliac and common iliac veins (sodium amytal anesthesia). The effect of occlusion of these veins is to be noted, both in reference to arterial blood flow and also the venous pressure in the limb. There was no increase in the arterial inflow after occlusion of the common iliac vein, nor was there any increase in the venous pressure. Compare these records with those in Fig. 8B.

In this series of experiments, the blood flow unit was placed in the usual manner on the iliac artery, the carotid artery was cannulated for the measurement of the arterial blood pressure, and one of the superficial veins of the lower leg was cannulated for measuring venous pressure. The blood flow at the normal venous pressure, before apply-



ing the tourniquet, was measured; then the tourniquet was inflated to a pressure of 40 mm. of mercury. This produced a rise in the venous pressure of the leg to 18 mm. of mercury within a minute. The blood flow in the iliac artery increased from a basal level of between 115 and 120 c.c. a minute to 150 c.c. a minute. When the tourniquet pressure was increased to 60 mm. of mercury the venous pressure rose to 40 and the blood flow increased to 205 c.c. a minute. The tourniquet pressure was then raised to 80, which brought the venous pressure up to 60 mm. of mercury and the blood flow to 250 c.c. a minute. The tourniquet pressure was further increased to 100 mm. of mercury, whereupon the venous pressure rose to 75 mm. of mercury and the blood flow increased to about 280 c.c. a minute. This was an increase of  $2\frac{1}{2}$  times the normal blood flow in the iliac artery. The tourniquet pressure was then raised to 120, which equaled the systolic blood pressure of the animal. Immediately after this increase the venous pressure rose to 83 mm. of mercury, but there was a rapid decrease in the arterial blood flow to the extremity (from 280 c.c. a minute to about 180 c.c. a minute). This was presumably because the high tourniquet pressure interfered with the arterial inflow. The tourniquet around the thigh was then completely released, and the venous pressure dropped back to the normal level of 5 mm. of mercury. The arterial blood flow first decreased to 90 c.c. a minute for about 20 seconds, and then returned to 120 to 125 c.c. a minute, which was practically the same volume flow as was recorded before the tourniquet had been applied. A continuous record of this experiment on one of the dogs is shown in Fig. 8B.

*Series 6. The Effect of Venous and Arterial Occlusion on the Blood Flow Through the Iliac Artery of the Unanesthetized Dog.*—The following experiments were carried out on one animal. A blood flow unit was placed on the right iliac artery, under aseptic precautions, using ether anesthesia. The animal was allowed to recover, and the following day he was brought to the laboratory and blood flow studies were made without anesthesia. One-half grain of morphine was given subcutaneously because the animal was restless and not well trained. There was considerable fluctuation in the normal blood flow level, depending on his emotional state, but for the most part it remained between 100 and 200 c.c. a minute. This rather low volume flow is to be accounted for partly by the fact that the deep femoral artery, which lay distal to the blood flow unit, was ligated at the operation.

First a pneumatic venous tourniquet was applied to the thigh, and the blood flow was measured before, during, and after the application. Reference to the record of this experiment (Fig. 9) shows that, when the normal blood flow was varying from 200 to 80 c.c. a minute, the application of the tourniquet increased the arterial inflow to approximately 400 c.c. a minute. This increase in arterial flow was maintained for the duration of the venous occlusion. There was some fluctuation in the flow which was associated with the restlessness of the animal. After

the release of the tourniquet, the arterial inflow quickly returned to about 150 c.c. a minute.

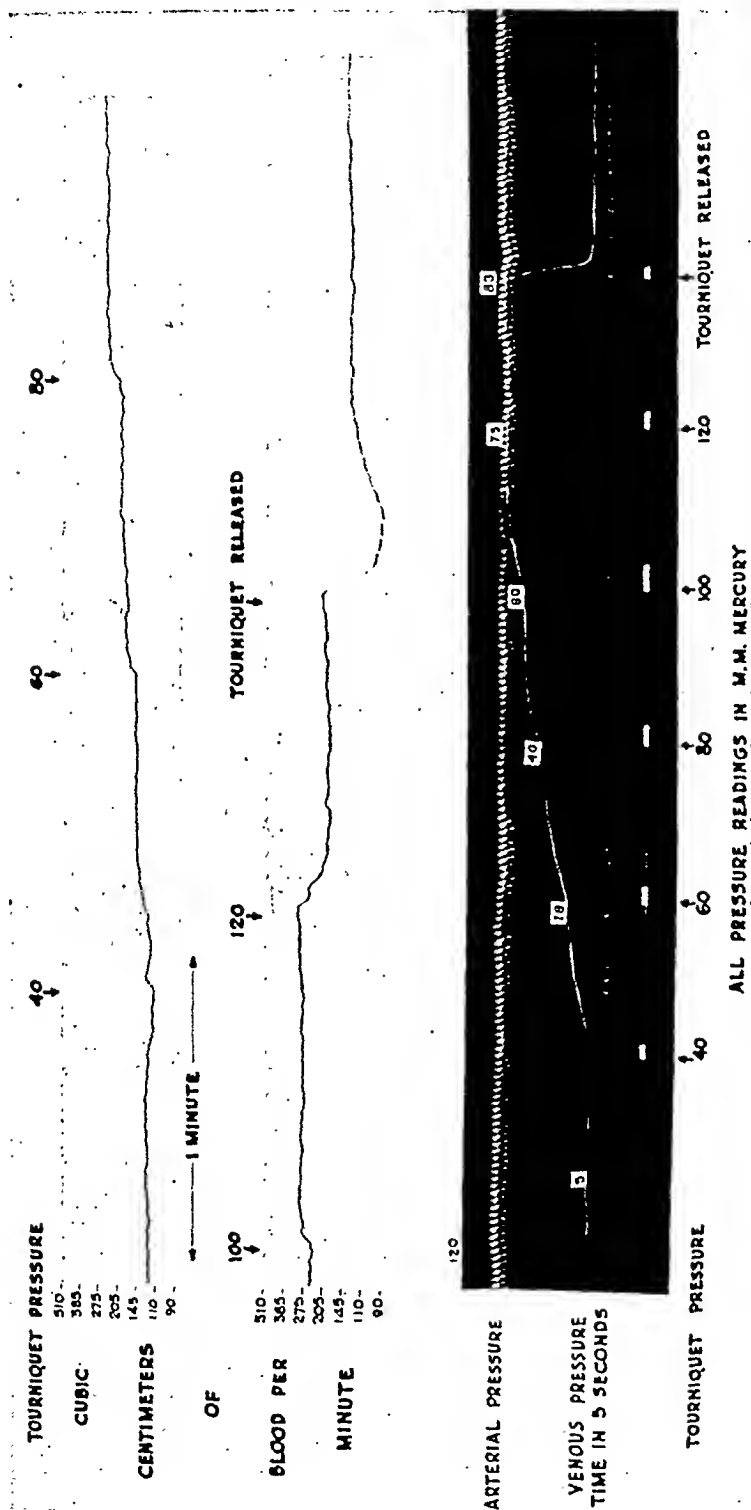


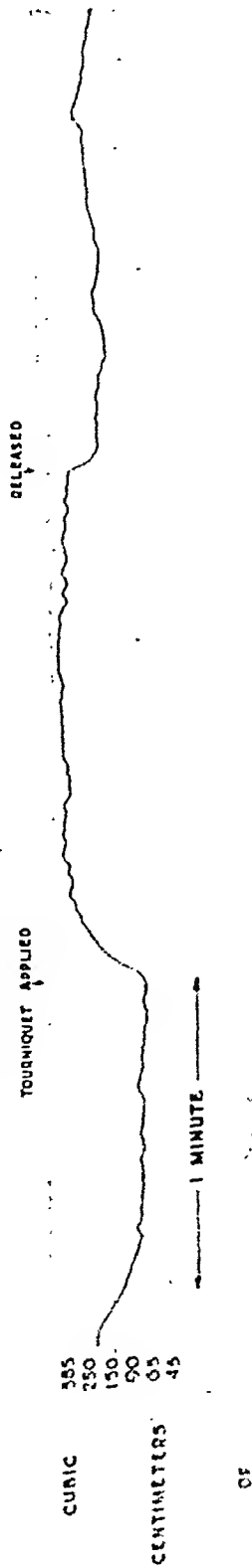
Fig. 8B.—The effect on the iliac artery blood flow of increasing venous pressures by means of a pneumatic tourniquet, applied to the thigh. It is to be noted in this record that, with each increase in the venous pressure of the extremity by raising the pressure in the tourniquet, there was an increase in the arterial blood flow until the venous pressure reached a level above 75 mm. of mercury. It will be seen that the venous pressure can be elevated much higher by this means than by ligation of the main vein of an extremity. The blood flow was increased by this means from 115 c.c. a minute to 280 c.c. a minute, whereas obstruction of the iliac vein in the same animal produced a rise from 115 c.c. a minute to only 215 c.c. a minute.

GOOD  
LEXINGTON, KY.

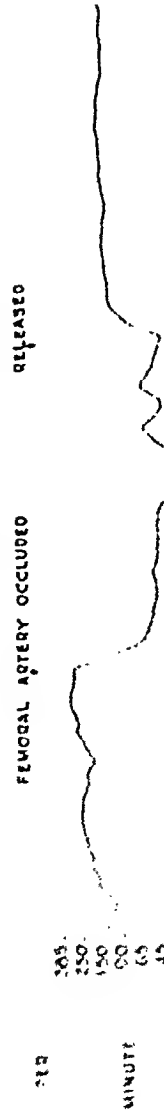
Then the femoral artery in the upper part of the thigh was occluded by digital compression (Fig. 9). It will be seen that this caused a

marked decrease in the volume flow through the iliac artery (from an average of 200 c.c. a minute to 45 c.c. a minute). This marked fall in arterial blood flow would be expected because of the fact that the deep femoral artery had been ligated at the time of operation, thus

A. VENOUS OCCLUSION WITH A PNEUMATIC TOURNIQUET ON THE THIGH



B. OCCLUSION OF THE FEMORAL ARTERY



\* DEEP FEMORAL ARTERY LIGATED

FIG. 2. The effect of venous and arterial occlusion on the blood flow in the iliac artery of an unanesthetized dog. Note that venous occlusion with a pneumatic tourniquet and obstruction of the femoral artery produced the same effect as when the animal is under ether or any other anesthetic. Compare these records with those in Fig. 1.

leaving a relatively small flow of blood in the iliac artery after occluding the femoral. The artery was released after one minute, and the arterial flow returned immediately to approximately 103 c.c. a minute. From this experiment it is readily seen that venous occlusion and arterial occlusion, without anesthesia, produced the same effects on the arterial inflow to an extremity as those which occurred under sodium amytal anesthesia.

#### DISCUSSION

Additional evidence concerning the therapeutic effect of venous occlusion on the arterial inflow to an extremity has been presented. This was obtained by means of a perfected thermostromuhr, with which it is possible to measure accurately the minute volume of blood passing through an artery or vein. Our investigations indicate that therapeutic venous occlusion does increase the arterial inflow to an extremity. By studying the blood flow in one extremity while venous occlusion was produced in the contralateral one, it was shown that the increase in the arterial blood flow is probably not caused by a humoral or nervous mechanism. However, further studies are needed to substantiate this view.

The effect of venous occlusion was found to be essentially the same, regardless of whether the arterial inflow was normal or deficient. The only difference was that, in the latter instance, the increase in the arterial blood flow developed more slowly. The effect of occlusion at various levels, by occluding, in the following order, the femoral and external and common iliac veins was studied. Simultaneous venous pressure records were made, and it was found that the increase in arterial inflow was directly related to the level of venous pressure. This was further corroborated by placing a pneumatic tourniquet around the thigh, and raising the venous pressure in steps by increasing, at intervals, the pressure in the tourniquet. By this means it was found that the arterial inflow increased with each increase in the pressure of the tourniquet until the level of the animal's systolic pressure was reached, at which point there was a falling off in the arterial blood flow despite a further increase in venous pressure. The paradox of having blood still flowing through the artery when the tourniquet pressure stands at the same level as the systolic pressure is explained by the fact that the thigh of a dog is uneven and oval, which makes it difficult to completely occlude the arterial blood supply by a pneumatic tourniquet unless very high pressures are used.

In the same animal, a comparison was made of the effect of occlusion of the common iliac vein, which carries most of the blood from the leg, with that produced by placing a pneumatic tourniquet about the thigh. It will be noted that after occlusion of the vein, the arterial inflow increased from 115 c.c. to 210 c.c. per minute, and that the venous pressure rose from 5 mm. of mercury to 25 mm., whereas, by means

of the pneumatic tourniquet, it was possible to raise the venous pressure from 5 mm. to 75 mm. of mercury, with a resulting increase in the arterial inflow from 120 c.c. to 280 c.c. a minute. These experiments indicate that producing venous occlusion by means of an adjustable pneumatic tourniquet increases the arterial inflow to an extremity to a greater degree than ligation of the main vein from the leg.

Since it is possible to increase the arterial inflow to a normal extremity after acute occlusion of its main arterial trunk, it seems justifiable to assume that, in chronic obliterative vascular disease, also, it can be increased by the same means, providing a certain amount of blood is reaching the extremity through collateral vessels. Thus, it appears most probable that the improvement in the circulation in the extremities of patients with obliterative arterial disease who have been treated with intermittent venous occlusion is to be at least partially explained by an increase in the arterial inflow during the period of venous occlusion. Reactive hyperemia apparently plays a minor role, if any, since it has been shown that the arterial blood flow returns very quickly to the preocclusion level after release of the tourniquet. For these reasons, it is recommended that, in the employment of intermittent venous congestion for the treatment of arterial insufficiency, a cycle in which the period of occlusion is longer than the period of release be used.

It is interesting to speculate on the mechanism of the increase in arterial inflow caused by venous occlusion. The following hypothesis, which is based on the foregoing experiments, is offered. The first effect of venous occlusion is to produce engorgement and dilatation of the veins. Next, dilatation of the venules, the capillaries, the arterioles, and the arteries occurs, in this order. This permits more blood to enter the vessels of the extremity because the increase in their diameter reduces resistance. In support of this view we have the original observations of Lewis and Grant,<sup>26</sup> who noted that venous occlusion increased the magnitude of the arterial pulsations. Additional evidence in favor of the above hypothesis is to be found in the experiment reported in Series 5 of this paper. There it was noted that the degree of increase in arterial inflow was directly related to the level of the venous pressure in the limb distal to the point at which the tourniquet was applied. Thus, it is suggested that the actual increase in arterial inflow comes about through this dilatation of the vascular tree. The higher the venous pressure, within certain limits, the greater the distention of the blood vessels which will result. Because of the enlargement of the blood channels, the peripheral resistance, despite the back pressure caused by the application of the tourniquet, is reduced; this permits a greater amount of blood to be forced through the vessels by the constant load of pressure on the arterial side. A diagrammatic sketch of this mechanism, produced by therapeutic venous occlusion, is shown (Fig. 10). Another possibility is that arteriovenous shunts may be

opened by the increased venous pressure, and so play a role. Other studies, which will be reported at a later date, are planned in an attempt to prove or disprove the above hypothesis.

### CONCLUSIONS

1. Therapeutic venous occlusion increases the arterial blood flow to an extremity.
2. The arterial inflow to a limb can be increased to a greater degree by means of a pneumatic tourniquet placed on the thigh than by occlusion of the main vein.
3. The increase in blood flow bears a direct relationship to the height of the venous pressure up to a certain level, above which the arterial inflow begins to decrease.

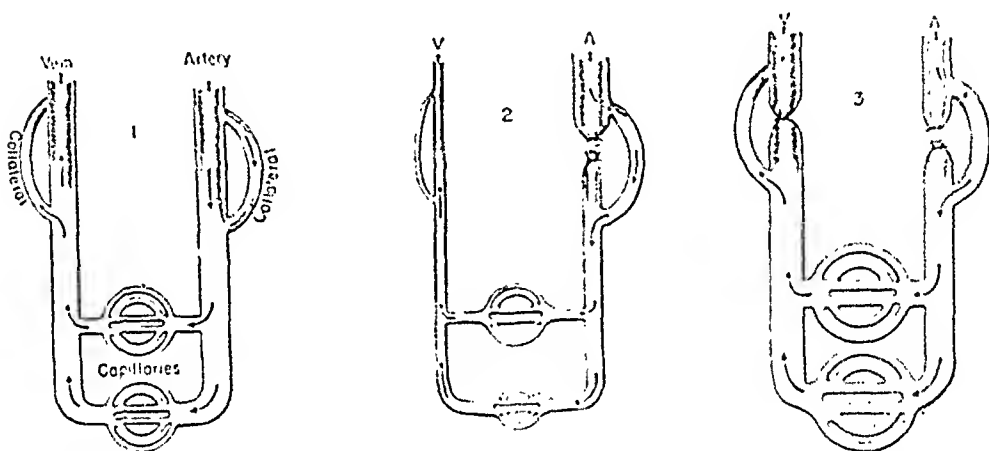


Fig. 10.—A schematic diagram showing the therapeutic effect of venous obstruction following acute arterial occlusion. 1. Normal artery, vein, capillaries, and collateral blood vessels; 2, the effect of ligation of the main artery, showing the decrease in size of the blood vessels distal to the ligature, indicating a decrease in arterial inflow to the limb; 3, the therapeutic effect of venous occlusion, showing dilatation of all of the vessels and capillaries, with a resulting increase in arterial inflow.

4. This study suggests that the benefit, in part, at least, which is derived from intermittent venous congestion in peripheral arterial insufficiency is a result of the increase in arterial blood flow which occurs during the period of congestion, rather than after the release of the tourniquet.

5. For this reason, in the treatment of arterial occlusion by intermittent venous congestion, it is recommended that the period of venous obstruction be longer than the period of release.

6. An explanation of the increase in arterial inflow to an extremity which is produced by therapeutic venous occlusion is suggested.

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## DISCUSSION

for years, particularly from the work of Minkins, Hohmann, Barney Brooks, and others, that vein ligation following sudden arterial occlusion would reduce the incidence of gangrene. It was shown by Rous that capillary permeability was increased during these periods of venous occlusion. It has been observed that the arterial bed is richer some weeks after venous occlusion. It has never been shown that the actual arterial inflow is increased in the presence of venous occlusion, and this morning we have seen very satisfactory evidence that it is.

This has therapeutic repercussions. Years ago I reported cases of vein ligation in the presence of arterial occlusion with satisfactory therapeutic results. We have means of intermittent or constant venous occlusion, and I believe that now we have a more rational basis for such therapy.

I should like to point out that, if it is true that the increased flow is caused by decreased resistance, then there must be other factors present, because the animals were under anesthesia. It is well known that anesthesia will remove any sympathetic vasospastic effect, so that there should be other mechanical factors in addition to this.

DR. NORMAN E. FREEMAN, Philadelphia.—I am really delighted to see this experimental work which confirms a clinical impression. If we observe the skin temperature of patients with thrombophlebitis, there is generally a higher skin temperature on the affected side. If the skin temperature is higher, that would indicate that there is an increase in arterial inflow, provided the blood is not simply shunted from the deep into the superficial venous system. With increased inflow there must be an increase in outflow, too, so that it is likely that there are collateral venous channels which are able to take the increase in the arterial inflow.

As far as the mechanism is concerned, Dr. Linton has suggested that it is purely mechanical, that is, that the back pressure on the veins causes dilatation which is then transmitted to the capillaries and to the arterioles, allowing larger inflow from the artery. A mechanical explanation is possible, but I do not think it is the entire story. The observations made by Lewis and Grant ten years ago on reactive hyperemia may throw some light on the mechanism of the increase in arterial inflow as the result of venous occlusion. They found that they could produce a reactive hyperemia in the tissues by venous obstruction, even temporary venous obstruction. Reactive hyperemia they considered as the repayment of a blood flow debt. The metabolism of the tissues continues unchanged, and with any deprivation of circulation some factor is produced in the tissues which causes a vasodilatation, so that for any degree of obstruction of inflow there is a compensatory increase afterwards.

It seems possible to interpret Dr. Linton's observations as indicative of a decrease in the supply of blood to certain tissues of the limb during the period of venous occlusion. During this period a chemical factor is released which will cause dilatation of the arteries.

This is a splendid piece of work and gives us some objective evidence to show the influence of venous occlusion on blood flow.

DR. NATHAN D. WILENSKY, Brooklyn.—I wish to thank Dr. Linton for his excellent presentation, and particularly for his beautiful experimental confirmation of the clinical observations which Dr. Collens and I have made on the use of intermittent venous occlusion in the treatment of peripheral arterial diseases.

We have always felt, just as Dr. Linton has so clearly demonstrated, that two factors play a part in the therapeutic value of intermittent venous occlusion. They are, first, the fact that during venous occlusion there is an increase in the rate of flow of blood through the major arterial pathways, and, second, and equally as important, is the increase in venous pressure which results in an increase in capillary pressure, thus favoring the diffusion of nutritional components through



the capillaries into the cells. This second phenomenon has, of course, been excellently presented by Landis in his studies on capillary pressure.

Although Dr. Linton did not observe reactive hyperemia with the release of venous occlusion, the work of Lewis and Grant still remains significant. If their observations are correct, there is a third, basic, physiologic factor which is partly responsible for the therapeutic value of intermittent venous occlusion. Just as Dr. Freeman has emphasized in his discussion, reactive hyperemia must be given time to come into play. It usually occurs about fifteen seconds after releasing the pressure, and its full effect may be observed for as long as two minutes.

Again I wish to say that I feel that Dr. Linton has made one of the most important contributions to the therapy of peripheral arterial diseases.

DR. LINTON.—I should like to say a word in reference to Dr. Pearce's remark about anesthesia. When operating on an animal under sodium amytal anesthesia, if one traumatizes the artery to the slightest degree, it becomes markedly constricted, whereas, if ether anesthesia is used, this does not occur. Thus, the barbiturates probably do not interrupt the sympathetic vasoconstrictor pathways.

I think the chief effect of venous occlusion is obtained during the period of occlusion because of the fact that the increase in arterial blood flow occurs at this time, and decreases as soon as the venous occlusion is released. I recently had a case in which I had to ligate both the external and internal iliac arteries in removing a large ovarian tumor, with the result that there was very little blood going into the limb. Following the operation I instituted intermittent venous congestion therapy, with nine minutes of occlusion and one minute without. It was by this means that I was able to get blood into the limb. Within two weeks and a half the patient was able to walk out of the hospital. It would seem that this case bears out my opinion that the chief benefit is derived during the period of occlusion, rather than following release of it.

## STUDIES ON PERIPHERAL BLOOD FLOW

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SINCE the beginning of our work on blood flow in animals about ten years ago, we have investigated many problems concerning the peripheral circulation of the dog. In this report a number of studies have been summarized, and, in some instances, additional data only recently obtained have been included. These studies will serve to illustrate the dynamic nature of the peripheral circulation, as reflected in the blood flow in the femoral artery or vein.

### TECHNICAL CONSIDERATIONS OF THE THERMOSTROMUHR

Since many readers may not be familiar with the thermostromuhr method of Rein or the direct-current thermostromuhr, it seemed advisable to devote the first part of the report to certain technical considerations.

In the preceding paper<sup>1</sup> on this program, studies on blood flow were described in which the Rein<sup>2</sup> thermostromuhr was used. Originally we made use of this method, but, after a careful analysis of certain thermal quantities, a thermostromuhr similar in principle was developed, in which diathermy plates were replaced by a direct-current heater. The modified method has all the advantages of the Rein technique, but has eliminated some of the disadvantages thereof, namely, the use of a high-frequency current and measurement of high-frequency resistance.

The fundamental principle underlying the Rein technique is illustrated schematically in Fig. 1. The high-frequency current is passed between the diathermy plates, heating the blood vessel and the blood. However, most of the heat is developed in the wall of the blood vessel, and this, in turn, affects the differential thermocouple, giving a definite relationship between the flow of blood and the deflection of the galvanometer. Fig. 2 shows the construction of a direct current thermostromuhr<sup>3</sup> with a heater, and a differential thermocouple as in the Rein unit.

The similarity of response of a high-frequency current unit and a direct-current unit is shown in Fig 3. This record was obtained by perfusing blood through a blood vessel. Note that the times required to bring the two units into equilibrium are practically identical.

When the deflections of the galvanometer and the corresponding flows are plotted on rectangular coordinate paper, the curve is a hyperbola for the usual range of flow. These data are obtained from records similar to those of Fig. 3, and are plotted on logarithmic paper (instead

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of rectangular coordinate paper) because the straight line is more convenient for checking subsequent calibrations for a given unit than a curve would be. The method requires careful calibrations for each unit before quantitative observations on blood flow in situ can be made. The question is often asked: "What effect does the thickness of the wall of the blood vessel have on the calibration curve?" We can answer this best by saying that calibrations on veins correspond to calibrations on arteries. We have units for which calibrations have remained relatively the same for a period of two and a half years when the calibrations have been made with veins as well as with arteries.

The reliability of the thermostromuhr has been checked in various ways. Recently, a type of flowmeter has been constructed in which the same principle is used as that which is employed in the thermostromuhr. The flowmeter consists of a bakelite tube which is inserted into the blood vessel by cannulation. This procedure, of course, necessitates the use of an anticoagulant. Nevertheless, it can be used simultaneously with the thermostromuhr on the same artery in situ for the purpose of checking results. Table I shows the results of such an experiment.

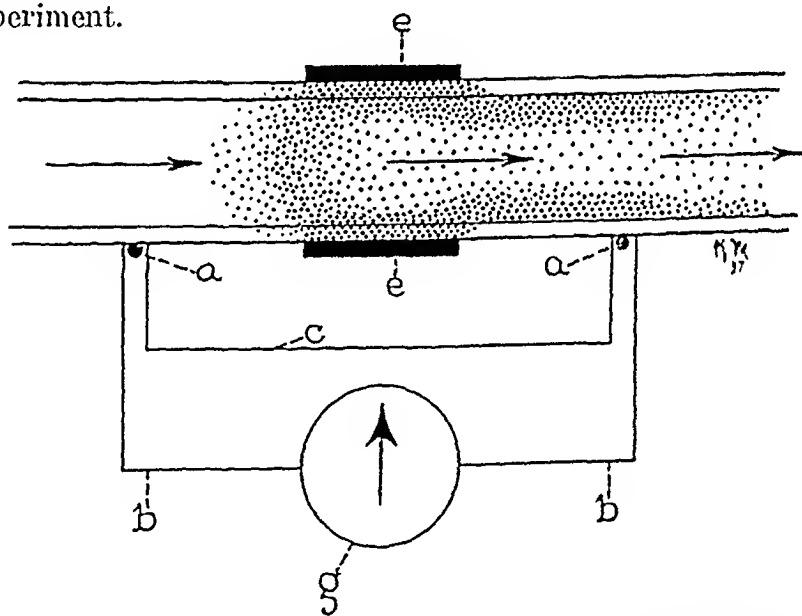


Fig. 1.—Schematic drawing of a diathermy-thermo-element applied to a blood vessel. *e, e*, Platinum electrodes; *a, a*, thermojunctions; *c*, constantan wire; *b, b*, wire per wire; *g*, galvanometer. Arrows indicate direction of flow of blood.

Technically, we are able to measure blood flow with an error of no more than 10 per cent when the flow is not turbulent. The units can be applied aseptically while the experimental animal is under the effects of anesthesia. After recovery of the animal from the operation, blood flow may be measured for an indefinite time.

#### PHYSICAL FACTORS THAT MODIFY BLOOD FLOW

Generally speaking, the flow of blood in a given blood vessel is proportional to the average blood pressure and inversely proportional

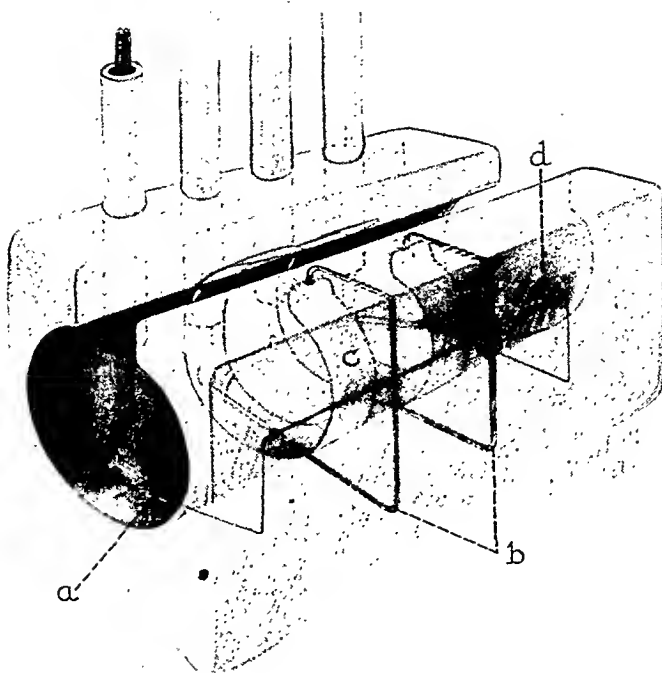


Fig. 2.—A thermostromuhr unit with direct-current heater. One of the thermo-junctions shown, at *a*, is made by soldering copper wire (0.0016 inch) to a constantan wire (0.002 inch) which is embedded in the groove *d*. The heating unit *c* consists of a folded loop of nichrome wire rolled into ribbon form and soldered to copper wires *b*.

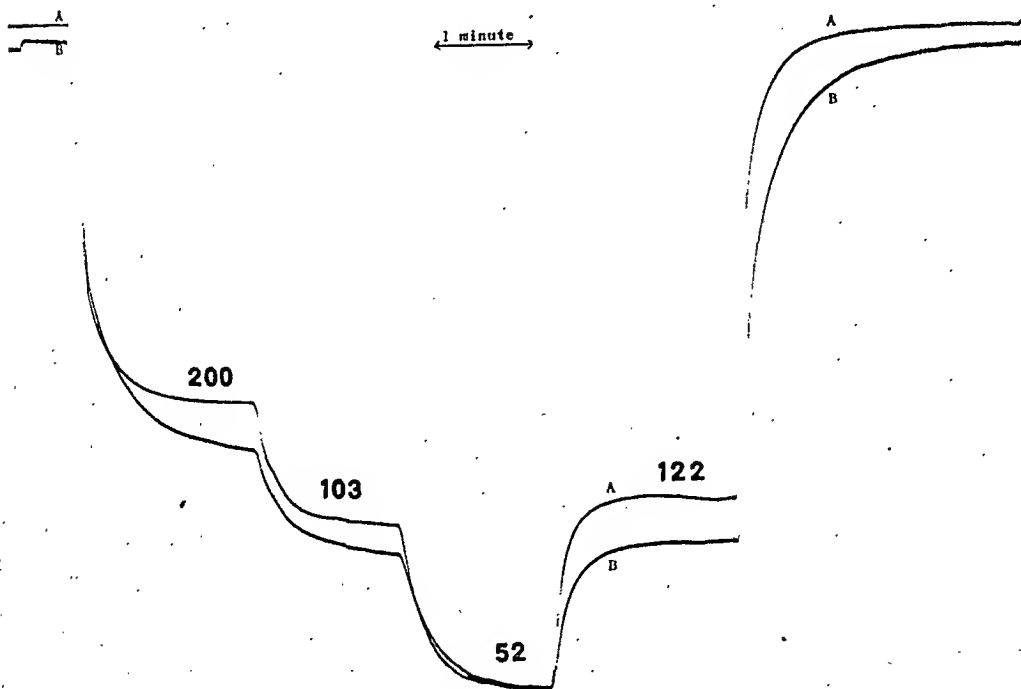


Fig. 3.—A comparison of the thermal equilibrium curves for the high-frequency unit (*A*) and the direct-current unit (*B*). The figures give the blood flow in cubic centimeters per minute. The deflection for each flow is the distance from the zero line to the horizontal portion of the curve.

TABLE I

A COMPARISON OF BLOOD FLOWS, AS MEASURED BY THE THERMOSTROMUHR, WITH THOSE RECORDED SIMULTANEOUSLY WITH A FLOWMETER

BLOOD FLOW (C.C. PER MIN.) IN CAROTID ARTERY	
BY THERMOSTROMUHR	BY FLOWMETER
187	205
210	227
245*	288
265	260
240	238
225	229
225	212
144	155
153	165
260	248

\*Equilibrium not fully established because of sudden fluctuation in blood flow.

to peripheral resistance. Hence, if the increase in average blood pressure is accompanied by an increase in peripheral resistance, there may be no alteration in flow. From observations of blood pressure alone, no conclusions may be drawn regarding changes in the flow of blood in any given vessel. Obviously, this is true when the various factors of the vasomotor system that maintain or regulate blood pressure are considered.

Similarly, a consideration of the velocity of blood flow does not provide an insight into values for the volume flow of blood unless the size of the cross section of the blood vessel can be ascertained. It might be well to point out the fact that the maximal velocity of laminar flow in tubes, blood vessels, and the like, is twice the average velocity and, consequently, that it is difficult to correlate "circulation time" with actual volume flow of blood.

Continuing the discussion of physical factors that modify blood flow, there is one factor in particular that we wish to emphasize; it is one that seems to have been misinterpreted in the past, namely, the relationship of reduction in the size of the lumen of an artery to the capacity of that vessel to transport blood. This factor has been investigated in vitro and in vivo, and with constrictive devices situated either inside or outside the vessel.<sup>4</sup> Table II shows the effect of introducing a bakelite

TABLE II

EFFECT ON THE BLOOD FLOW OF INTRODUCING CONSTRICTING UNIT (8.0 MM. LONG) INTO AN ARTIFICIAL CIRCULATORY SYSTEM AND INTO THE CAROTID ARTERY OF AN ANESTHETIZED, HEPARINIZED DOG. (THE ORIGINAL DIAMETER OF THE LUMEN IS 3.00 MM.)

PER CENT DECREASE IN		PER CENT DECREASE IN BLOOD FLOW		
DIAMETER	AREA	GRAVITY SYSTEM	DALE-SCHUSTER PUMP SYSTEM	ARTIFICIAL SYSTEM
17	31	2	0	1
35	58	7.5	0	3
48	73	17	1.5	18
54	79	50.5	24	24
67	89	58	49	44.7
80	96	68.5	79	71

constrictive device 8 mm. long *into* a blood vessel. If the size of the lumen is reduced from 3 to 1 mm., thereby reducing the effective area of cross section to 11 per cent, the blood flow will still remain more than one-half of what it originally was. Similar results were obtained when the lumen of the blood vessel was reduced by placing constrictive devices on the outside of the vessel.

#### BLOOD FLOW IN THE EXTREMITY IN THE TRAINED DOG

The studies on peripheral circulation reviewed under this title include those which were carried out under natural conditions. No operation except that necessary for the application of the thermostromuhr was performed and no drugs were injected. These studies serve as a contrast to those to be discussed later, in which natural conditions have been altered by the investigators.

*Rhythmicity.*—Our interest in rhythmic variations in blood flow was aroused by two independent studies which were being conducted at about the same time. One of us (Balde) was studying the blood flow to the finger by means of a plethysmograph. The photographic records made during this study showed rhythmic variations of considerable magnitude in a resting man. An intensive study of the blood flow in the spleen<sup>5</sup> of the trained dog was the other investigation in progress at this time. The flow was measured by the thermostromuhr method. The well-known "splenic rhythm" was present in almost all of the records of blood flow, and was particularly pronounced following a sudden noise or an intravenous injection of epinephrine. This "splenic rhythm" was studied by recording, simultaneously, the volume of the spleen, the flow of blood in both splenic artery and splenic vein, and the blood pressure. We concluded that the rhythm was not caused by rhythmic contractions of the splenic musculature or by variations in systemic blood pressure, but, rather, by rhythmic variations in the vascular bed. In an attempt to determine the cause of this rhythmicity, a careful study was made of the phenomenon in the extremities of the dog. Blood flow was measured in the femoral artery, and the volume of the leg was recorded by means of a very sensitive plethysmograph. Simultaneously, the mean blood pressure and respiration were also noted. The rhythmic variations in volume of the leg paralleled those in blood flow, but were usually independent of blood pressure and respiration.

Fig. 4 shows the rhythmic variations in the flow of blood in the femoral artery, and indicates the difficulty which may be experienced in determining the normal or basal flow. This record was made on a trained dog, and shows the comparison between variations in blood flow, as indicated by the thermostromuhr, and the changes in volume, as recorded by a plethysmograph.

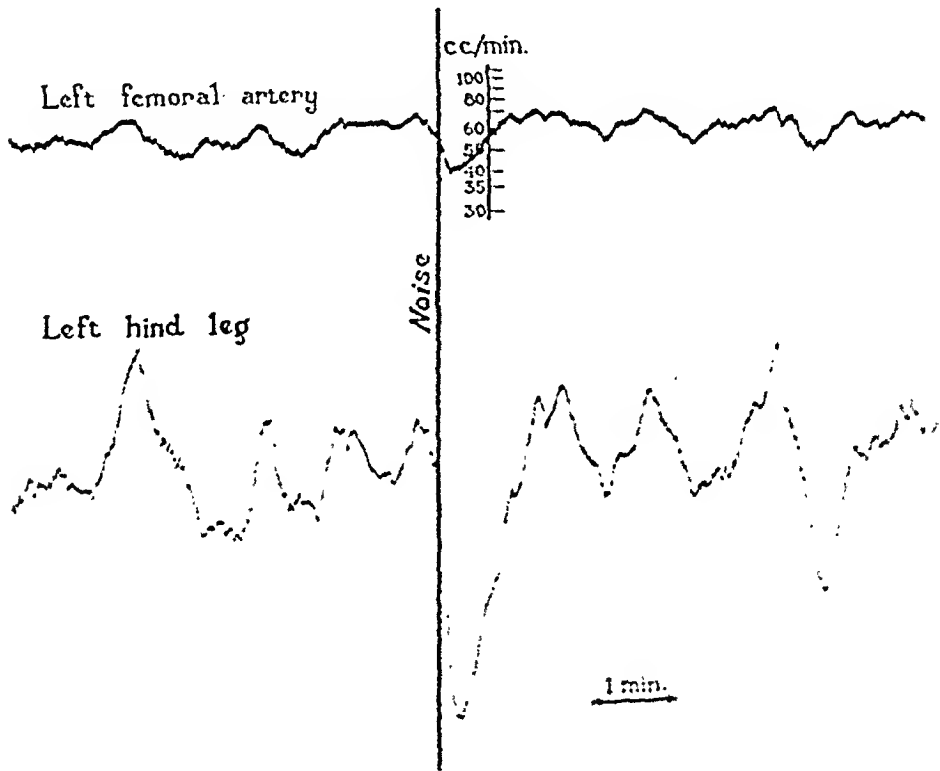
*Exercise.*—The effect of exercise on the flow of blood to the muscle is well known. Actual quantitative observations on the flow in the femoral or common iliac artery, as well as in other blood vessels, of the

trained dog have been made during natural exercise of the animal and recorded photographically while the dog was walking on the treadmill at the rate of three miles per hour.<sup>6, 7</sup> The flow increases immediately at the onset of exercise. The results of a series of experiments are shown in Table III.

TABLE III  
EFFECT OF EXERCISE ON BLOOD FLOW

DOG	WEIGHT (KG.)	ARTERY	BLOOD FLOW (C.C. PER MIN.)		
			CONTROL	DURING EXERCISE*	AFTER EXERCISE
1	18.4	Femoral	99	416	168
2	11.6	External iliac	58	295	86
3	14.4	Common iliac	215	995	262
4	17.8	Common iliac	184	735	292
5	15.0	Common iliac	235	935	429
6	20.6	Common iliac	305	1000	328
7	12.2	Femoral	147	498	193

\*Walking on horizontal treadmill at 3 miles per hour.



F

h

v

f

as great as 100 per cent. Fig. 5 shows the typical results of observations on the femoral artery. These results were contrary to previously existing opinions, which had been developed on the basis of indirect evidence. They were confirmed in the human being by Burton and Murlin,<sup>9</sup> who used the Thermal Circulation Index for indicating blood flow.

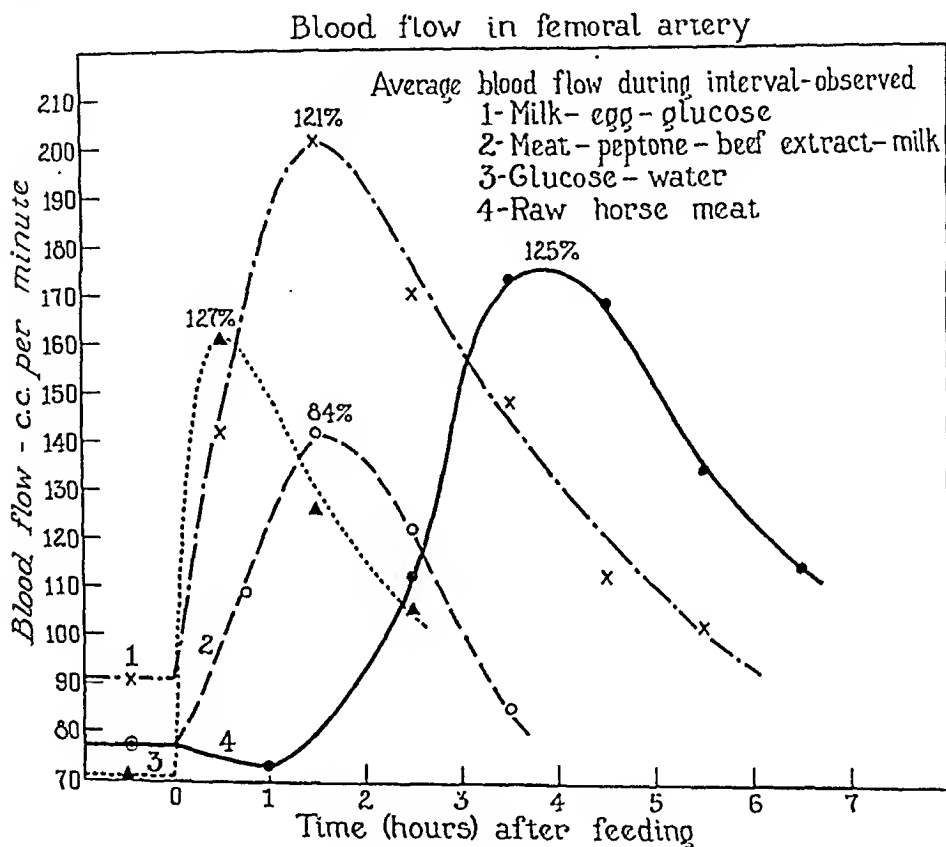


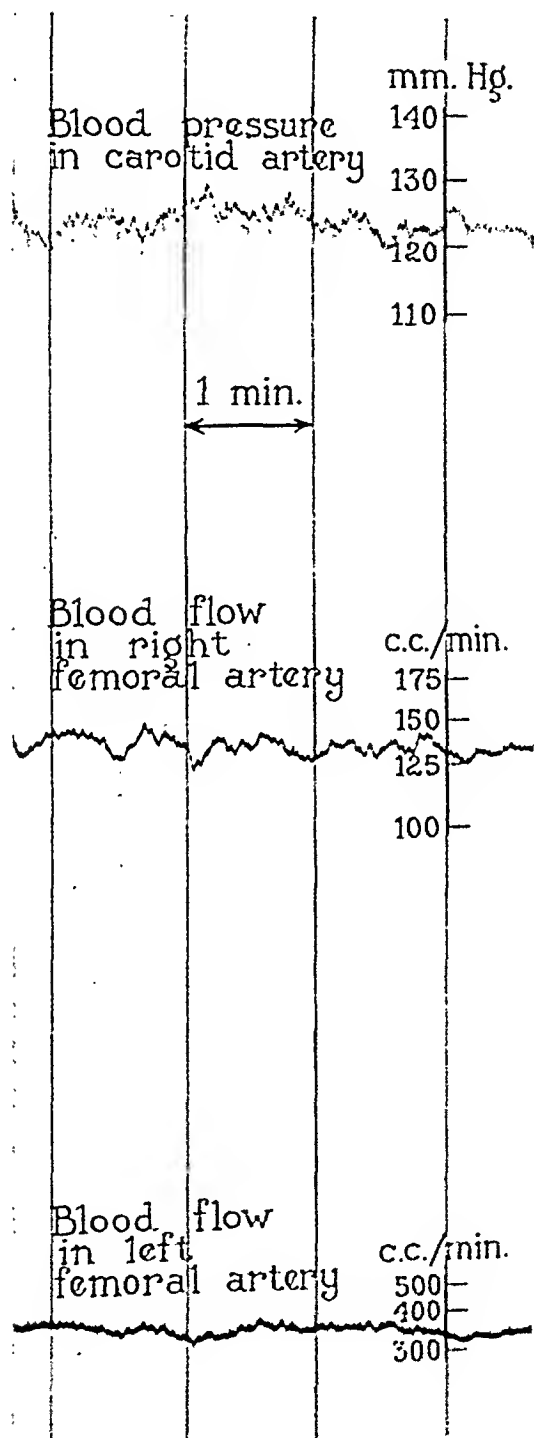
Fig. 5.—The effect of meals on the blood flow in the femoral artery of the dog.

#### BLOOD FLOW IN THE EXTREMITY UNDER ALTERED CONDITIONS

*Anesthetic Agents.*—The flow of blood in the femoral artery is increased markedly during surgical anesthesia induced by ether. At the same time, the blood pressure either remains the same or is increased slightly. Our first observations on the effect of lumbar sympathectomy on the femoral blood flow were made while the experimental animals were under the effects of ether anesthesia, and we failed completely to detect any effect caused by unilateral removal of the entire sympathetic chain from the level of the second lumbar vertebra. We suspected that the failure to detect any change in flow was referable to the anesthetic agent employed. This failure to detect the effect of sympathectomy on the blood flow in the femoral artery marked a turning point in our investigations on the flow of blood. A unit that could be sterilized by boiling was constructed, and all subsequent studies, when desired, have been made on trained dogs.



*Sympathectomy.*—After establishment of the fact that the simultaneous blood flow in both femoral arteries is approximately the same under resting conditions in the trained dog, unilateral sympathectomy



the units were applied while the animal was under the effects of a procaine type of anesthetic agent (pontocaine hydrochloride), administered by local infiltration. The blood flow in the artery on the denervated side was about double that on the innervated side.<sup>10</sup> This effect has persisted as long as two years and ten months. This marked difference in flow promptly disappeared when the animal was anesthetized with ether.

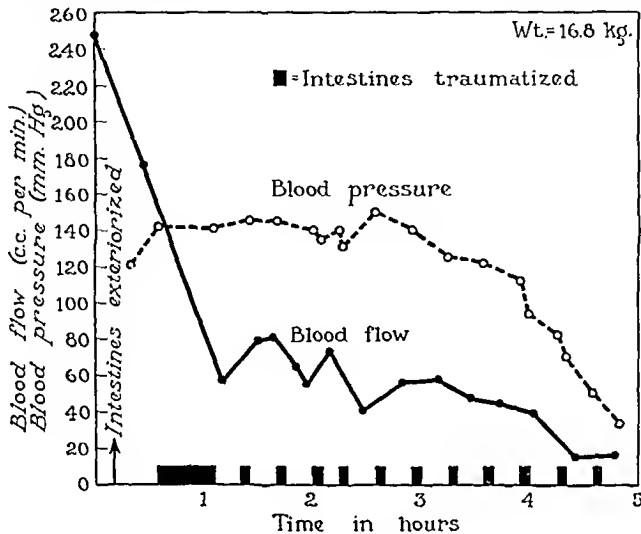


Fig. 7.—Results of a typical experiment in which shock was produced by manipulation of the intestines.

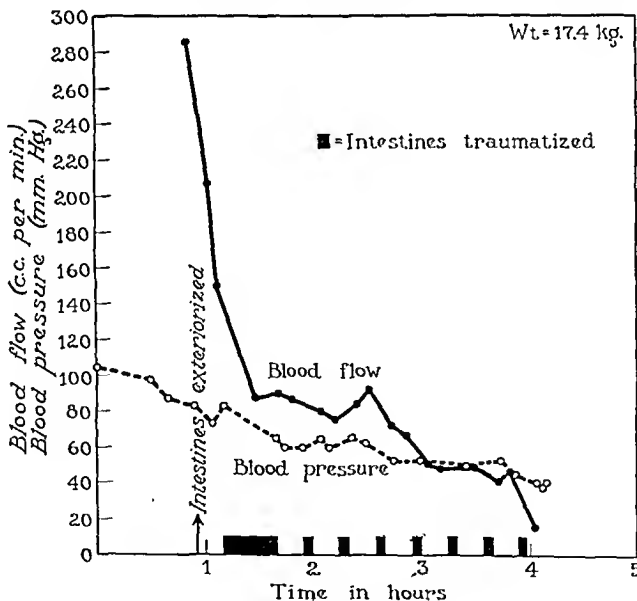


Fig. 8.—Results of experiment similar to that represented in Fig. 7, on a different animal.

Fig. 6 shows a record of blood flow in both femoral arteries, recorded simultaneously with mean blood pressure in the earotid artery, of a trained dog on which left lumbar sympathectomy had been done nine months previously. This record gives the necessary data for calcula-

tion of the index of peripheral resistance in each femoral artery, that pressure is, ———. The index of peripheral resistance in the femoral artery flow

on the innervated side is about two and a half times that in the artery on the denervated side in this particular experiment.

*Traumatic Shock.*—In the production of shock by manipulation of the intestines, the flow of blood in the femoral artery is reduced markedly and rapidly. The blood pressure may be maintained for some time above what might be considered a good physiologic level. Finally, after successive manipulations of the intestines at intervals, the blood pressure reaches a shock value; the flow of blood in the femoral artery decreases more markedly; and the dog dies shortly thereafter. Figs. 7 and 8 illustrate these results.

*Thyrotoxicosis.*—If dogs are fed desiccated thyroid gland or are given thyroxine, symptoms of thyrotoxicosis develop. In the presence of this condition, the flow of blood in the femoral artery may be increased threefold.<sup>11</sup>

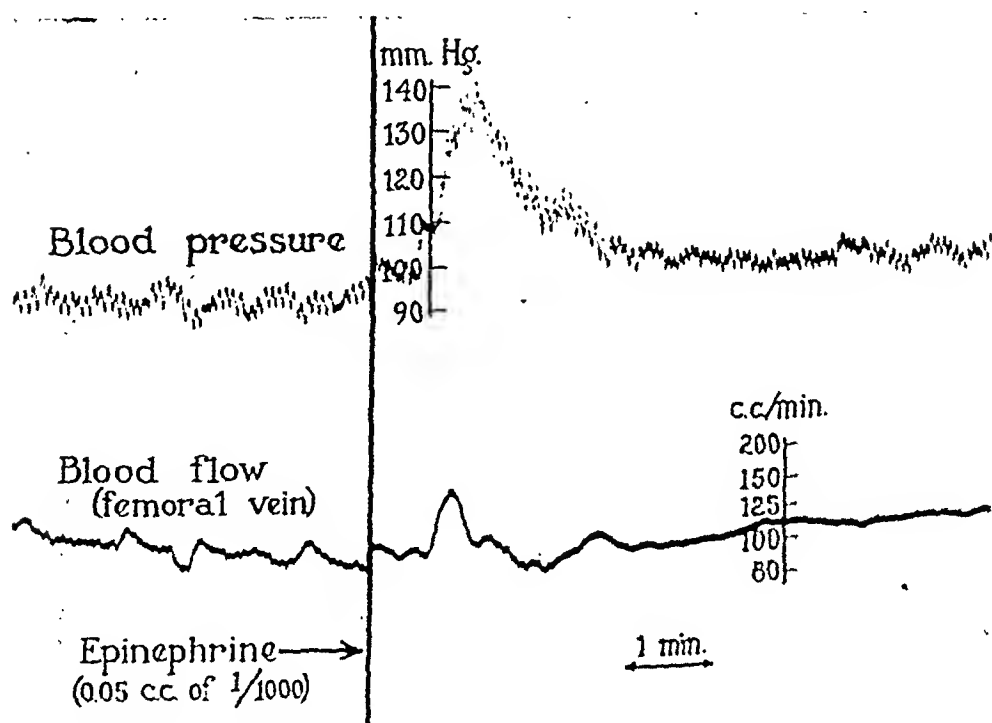


FIG. 9.—The effect of an intravenous injection of 1:1,000 solution of epinephrine (0.05 c.c.) on the blood flow in the femoral vein and on the mean blood pressure in the carotid artery of the trained dog.

*Drugs.*—The effect of intravenous injections of, say, 0.05 c.c. of a 1:1,000 solution of epinephrine is not always the same on the flow of blood in the femoral blood vessels. The result may be an increase, a decrease, or no significant change, according to the resultant effect of the various factors controlling blood flow. The change in blood flow

referable to epinephrine is very transient. Fig. 9 illustrates an effect produced on the flow of blood in the femoral vein and the blood pressure in the carotid artery.

*Pressor and Diuretic-Antidiuretic Principle of Posterior Lobe of Pituitary Body (Pitressin).—*When pitressin is administered subcutaneously or intramuscularly, it exerts no significant effect on the blood flow. However, if it is administered intravenously, its effects are the most dramatic of those of any drug that we have observed. The effect on every blood vessel which we have studied thus far is a *marked decrease* in flow. The flow in the femoral artery or vein decreases as much as 90 per cent, and remains decreased for several minutes, when 1 pressor

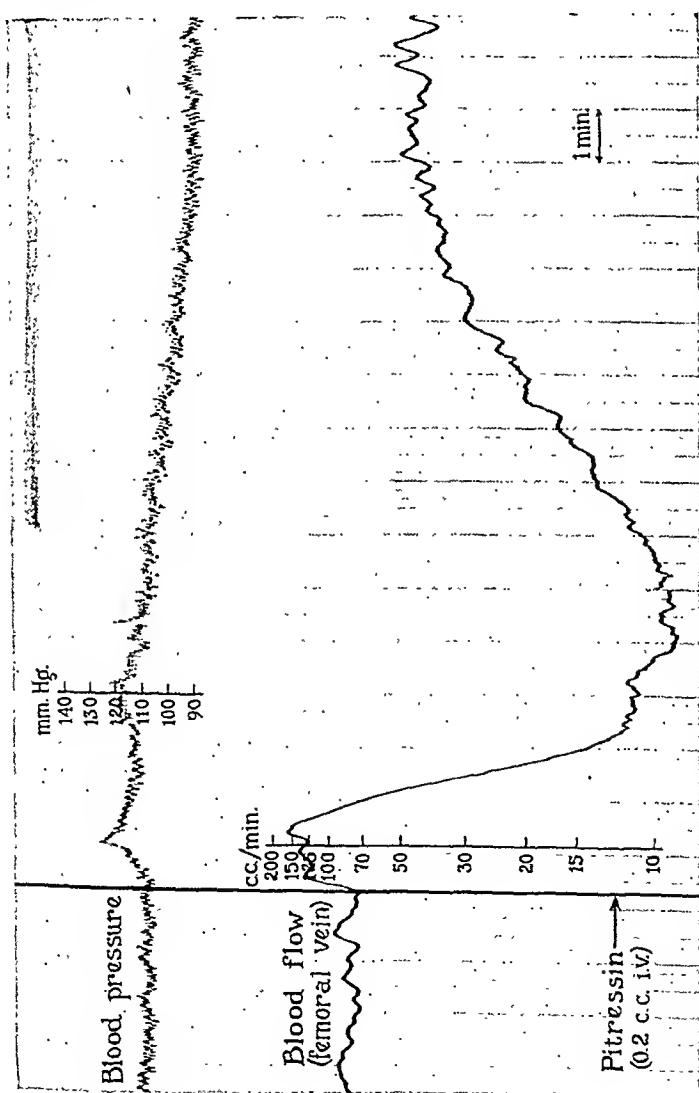


Fig. 10.—The effect of an intravenous injection of pitressin (0.2 c.c.) on the blood flow in the femoral vein and the mean blood pressure in the carotid artery of the trained dog.

unit is injected intravenously.<sup>12</sup> Frequently, the flow does not attain the preinjection value until sixty or more minutes have elapsed. The effect of pitressin is not entirely peripheral, for it is accompanied by a

marked slowing of the pulse rate and by either no increase or only a moderate increase in blood pressure. Fig. 10 shows a typical result of the injection of pitressin.

#### SUMMARY AND CONCLUSIONS

Using a thermostromuhr, we have been able to measure the flow of blood in large arteries or veins of the peripheral vascular system of the trained dog under various conditions. It is our hope that the data presented will serve to emphasize the fact that the blood flow to an extremity is influenced by many factors, any one of which, if altered, may profoundly affect the flow of blood to that region.

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We have also noticed that, shortly after applying the clamp to a renal artery or the aorta, the vessel itself thins out under the clamp so that much more blood gets through than one might anticipate. In other words, the pressure against the clamp causes thinning within the clamp, allowing more room for the blood to get through.

DR. LOUIS N. KATZ, Chicago.—The Mayo group is to be congratulated on their excellent report on this important subject. It must be emphasized, as they have shown, that the blood pressure, blood flow, velocity of flow, and circulation time are not interdependent, but are independent of each other. One of these factors may change without affecting the others. Consequently, when investigating changes in the circulation, one must take care not to draw too many deductions regarding the other variables from a change in one.

The circulation in the peripheral vessels of the limb, as in any vessel, is complicated, and only by the application of methods and correlations such as those reported in this communication can our knowledge of the circulation in blood vessels be enhanced.

# THE VASODILATING ACTION OF VARIOUS THERAPEUTIC PROCEDURES WHICH ARE USED IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE

## A PLETHYSMOGRAPHIC STUDY

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**I**N VIEW of the conflicting reports as to the efficacy of the therapeutic agents commonly employed in the treatment of peripheral vascular disease, the vasodilating action of some of these procedures was investigated by means of the venous occlusion plethysmographic method. With this method the total blood flow to a portion of an extremity can be measured, and hence any alteration in flow produced by a drug or a procedure becomes apparent and can be expressed quantitatively.

### METHOD

The study was performed upon thirty-one patients who were suffering from various types of peripheral vascular disease (chiefly thromboangiitis obliterans and Raynaud's disease), upon thirteen patients with various mental states (schizophrenia, mental deficiency), and upon thirty-four normal subjects. Some of the subjects were used for testing the effect of more than one drug. Blood flow measurements in c.c. per minute per 100 c.c. of limb volume were obtained according to the technique previously described.<sup>1</sup> The bath temperature (temperature of the water in the plethysmograph) was maintained at 32° C., and the room temperature between 25° and 27° C. The procedure which was generally followed consisted of placing a hand and a contralateral leg, forearm, or foot into plethysmographs, and recording control blood flow readings in two extremities for about a half hour. The drug was then administered by the appropriate route, or the procedure under study was begun, and blood flow readings were taken at 10-minute intervals for one to three hours, depending upon the rapidity with which changes in blood flow were observed. It was inadvisable to continue the test for more than 3½ hours because the subjects generally became restless beyond this point, which made further observations unreliable. The onset and duration of the various symptoms which resulted from the administration of the drugs were noted, and the blood pressure and pulse rate were recorded at intervals during the experiments.

### RESULTS

Calcium Gluconate, "Padutin," Papaverin, "Spasmalgin,"  
Thiamin Chloride.

*Calcium Gluconate.*—Weichsel<sup>2</sup> has recently reported that the intravenous injection of calcium gluconate in cases of peripheral occlusive arterial disease was followed by alleviation of pain and an increase in ability to walk. He concluded that the response was caused by the

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vasodilator effect of calcium on the parasympathetic or antisympathetic mechanism. Accordingly, we tested this drug on six subjects by injecting 2.75 Gm. intravenously and noting the effect upon the peripheral circulation. In five of the six subjects no change in blood flow was noted in the hand or leg, but in the remaining case the flow in the hand was approximately doubled, and remained elevated for about forty minutes.

*Padutin.*—The use of various tissue extracts in the treatment of peripheral vascular disease has been advocated by a number of authors.<sup>3-6</sup> One of these substances, "Padutin," a deproteinized pancreatic extract, was found by Frenkel<sup>7</sup> to dilate peripheral vessels and to increase their permeability. Werle and Multhaupt<sup>8</sup> reported that, after intramuscular and intravenous injection of this substance, the skin temperature of the finger tips was elevated. We tested the vasodilator effect of "Padutin" by injecting 4 "biologic" units intramuscularly in a series of seven subjects. In no instance was a change in blood flow to either the hand, leg, or forearm observed over a period of 80 to 100 minutes following its administration.

*Papaverin and "Spasmalgin."*—Mulinos and his associates<sup>9</sup> have recently reported that the intravenous injection of papaverin hydrochloride in cases of Raynaud's disease was followed by an increase in the rate of blood flow to the hand, as well as complete alleviation of the cyanosis and pain caused by exposure to cold. Littauer and Wright,<sup>10</sup> however, concluded that this drug is less effective in causing vascular relaxation than immersing an extremity in warm water. We investigated the vasodilator effect of papaverin hydrochloride ( $\frac{1}{2}$  grain) and the proprietary substance "Spasmalgin," which contains pantopon and atropine, as well as papaverin, upon seventeen patients who were suffering from either thromboangiitis obliterans, scleroderma, or hypertension. With both these substances there was either no change or only a slight increase in flow to the hand, except in one case in which the blood flow was doubled and remained elevated for about forty-five minutes. In the foot, very little response was observed in any of the experiments.

*Thiamin Chloride.*—Since thiamin chloride has been used with some degree of success in alleviating rest pain of ischemic origin,<sup>11</sup> it was thought of interest to ascertain whether or not this drug has any vasodilating properties. In a series of five subjects there was very little effect on the blood flow to the hand, leg, and foot after the intravenous administration of 10,000 to 20,000 units. In contrast with these observations was the effect of nicotinic acid,<sup>12</sup> which is another fraction of the vitamin B complex. In a series of fifteen normal subjects, the oral administration of 100 to 300 mg. of nicotinic acid produced a significant augmentation in flow to the hand and forearm, averaging 2.3 times the control level. The increased flow with a single dose lasted for approximately seventy minutes.



*Generalized Effects.*—The administration of "Padutin" and thiamin chloride was followed by no subjective symptoms, whereas with calcium gluconate a generalized feeling of warmth, together with a flushing of the face and neck, was usually experienced. Papaverin generally produced no symptoms or occasionally a fleeting headache; with "Spas-malgin," headache was much more common, and was associated with a sensation of dizziness. All four drugs had little effect upon blood pressure or pulse rate.

#### Alcohol, Stilbestrol, Prostigmine

*Alcohol.*—Since it is well known that alcohol causes a rise in skin temperature, particularly of the finger tips, and an increase in oscillations, it was decided to obtain a quantitative measure of the vasodilator effect in a series of seven subjects. Whiskey, in 60 to 80 c.c. doses, was given orally, and blood flow readings were taken for the subsequent 80 to 110 minutes. Fig. 1 shows a typical response; an increase in blood flow was generally observed in the hand (about two times the control level), and little or no effect in the leg or forearm. These observations are in accord with those of Silbert and his associates,<sup>12</sup> who used skin and muscle thermocouples.

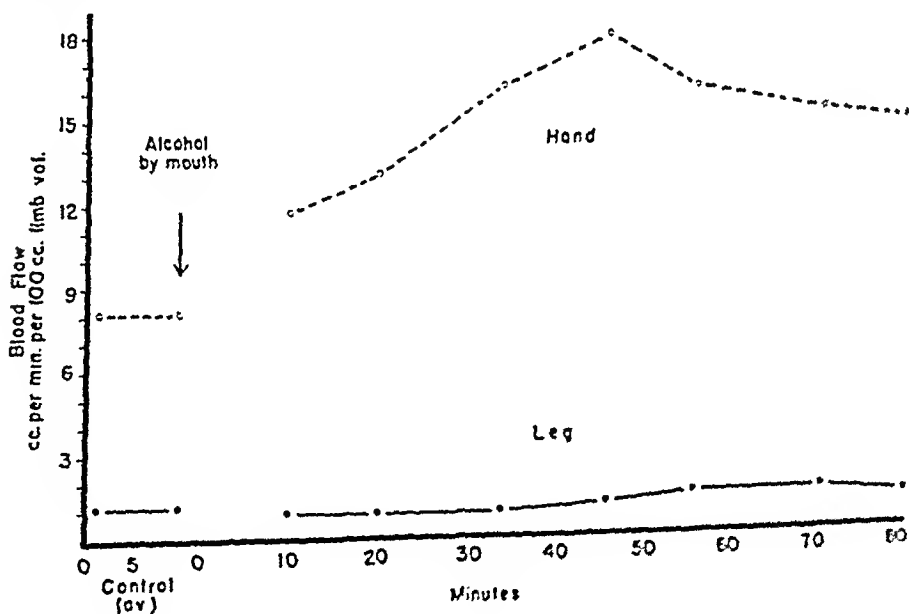


Fig. 1.—Effect of the oral administration of 60 c.c. of whiskey.

and the duration of the increase averaged seventy-five minutes. It is necessary to point out, however, that all of the subjects in this group had low control flow readings in the hand as a result of vasoconstriction of nervous origin. In all five instances there was no significant increase in flow in the forearm. In contrast with these results, estrin or theelin, in dosages of 2,000 international units, produced no change in blood flow to either the hand or forearm.

*Prostigmine.*—The fact that prostigmine has an inhibitory action upon choline esterase, thus permitting an unimpaired action of acetylcholine, led Perlow<sup>17</sup> to investigate its effects upon the peripheral circulation. He found that a significant increase in the skin temperature of the digits and a definite acceleration of capillary blood flow resulted from the administration of this drug. We studied the effect of the intramuscular injection of 0.5 mg. and the oral administration of 15 mg. of prostigmine methylsulfate in a series of seven subjects. The flow in the hand in four instances showed an increase which ranged from 1.5 to 2.5 times the control level, but there was no change in the remaining three. In the forearm the flow was approximately doubled in two instances and unaffected in the remaining five.

*Generalized Effects.*—The administration of prostigmine induced no symptoms; stilbestrol and alcohol produced a feeling of warmth and some flushing of the face. Stilbestrol caused a fall in systolic blood pressure which averaged 10 mm. Hg., but the other three drugs had little effect in this respect.

#### HYPERTONIC SALINE SOLUTION, HISTAMINE

*Hypertonic Saline Solution.*—Silbert,<sup>18</sup> Samuels,<sup>19</sup> and others have advocated the use of large quantities of 5 per cent saline solution in the treatment of thromboangiitis obliterans. Friedlander and her co-workers<sup>20</sup> reported a definite increase in both the skin and muscle temperature of the lower extremities following its intravenous administration. We tested the vasodilating action of hypertonic saline solution (250 c.c.) on a series of twenty-one subjects, sixteen of whom had thromboangiitis obliterans; the other five were normal. During the period of injection (which generally lasted from twenty to twenty-five minutes), and for the subsequent 60 to 100 minutes, the blood flow in the hand was found to be unchanged or slightly increased in fifteen trials, and significantly increased in the remaining six. Fig. 2 is typical of the response when there was an augmentation in flow in the hand. In the leg, which was tested five times, there was either no change or a slight increase in two trials, and a definite increase in the remaining three. In the foot, during the period of injection, there was either no change or a slight increase in flow in eight of fourteen experiments, and a significant augmentation in the remaining six. However, after the injection was completed the increased flow to the foot persisted in only three instances (for an average period of 80 minutes). Physiologic

saline, which was tested under similar conditions, had little or no effect upon blood flow through the hand and foot, even during the period of administration.

*Histamine.*—Kling and Sashin<sup>21</sup> and others have reported excellent results with histamine iontophoresis in such conditions as Raynaud's disease, aeroparesthesia, and thromboangiitis obliterans. The vasodilating effect of this drug, using the intravenous route, was investigated in a series of twelve subjects. From 0.3 to 0.5 mg. of histamine acid phosphate, dissolved in 10 c.c. of saline, was administered over a period of seven to ten minutes. In the hand, during the time of injection, there was a significant increase in flow (about two to three times the control level), which, in half of the trials, persisted for about fifteen to twenty minutes after the injection was completed. In the remaining instances the flow returned to the control level quickly. In the case of the leg there were marked variations in flow during the period of administration, and then a return almost immediately to the previous level (Fig. 3). It is obvious that these results cannot be compared with those reported by authors<sup>21</sup> who employed iontophoresis.

*Generalized Effects.*—Hypertonic saline produced practically no symptoms except the occasional complaint of a feeling of thirst. Histamine generally caused a feeling of warmth and flushing of the face and a transient throbbing headache; these symptoms were for the most part limited to the period of administration. The latter drug generally caused an elevation of both systolic and diastolic blood pressure during the injection phase, but the pressure returned to the control levels almost immediately afterward (Fig. 3). In some instances, with histamine, a drop in pressure was observed during the period of administration. The pulse rate varied, but in no constant direction. With hypertonic saline solution, the blood pressure and pulse rate responses were slight and inconsistent.

#### INTERMITTENT VENOUS OCCLUSION

The procedure which has probably had the most extensive clinical trial in recent years in the treatment of peripheral vascular disease is that of intermittent venous occlusion. Collens and Wilensky,<sup>22</sup> who popularized it, and other investigators, including Kramer,<sup>23</sup> Brown and Arnott<sup>24</sup> and de Takats and his associates,<sup>25</sup> regard this procedure as beneficial. On the other hand, Veal and McFord,<sup>26</sup> Allen and McKeehnie,<sup>27</sup> Wright<sup>28</sup> and others believe that the value of the treatment has not been definitely established. The rationale of the method is based upon the work of Bier<sup>29</sup> and of Lewis and Grant.<sup>30</sup> According to the latter authors, the application to an extremity of pressures definitely below the level of systolic pressure produces a state of reactive hyperemia.

We tested the vasodilating action of such a procedure by intermittently applying a pressure of 70 mm. Hg (two minutes on and two

minutes off) for periods of two to three hours; blood flow measurements were made every fifteen minutes. Eleven subjects were used; five of them complained of intermittent claudication, and the remainder were normal. In no instance was a sustained increase in blood flow observed in the leg or forearm during or following this procedure. In the hand and foot, a slight increase occurred in three trials. Whether or not there was an augmentation in flow during the period in which the high venous pressure was maintained could not be ascertained by the

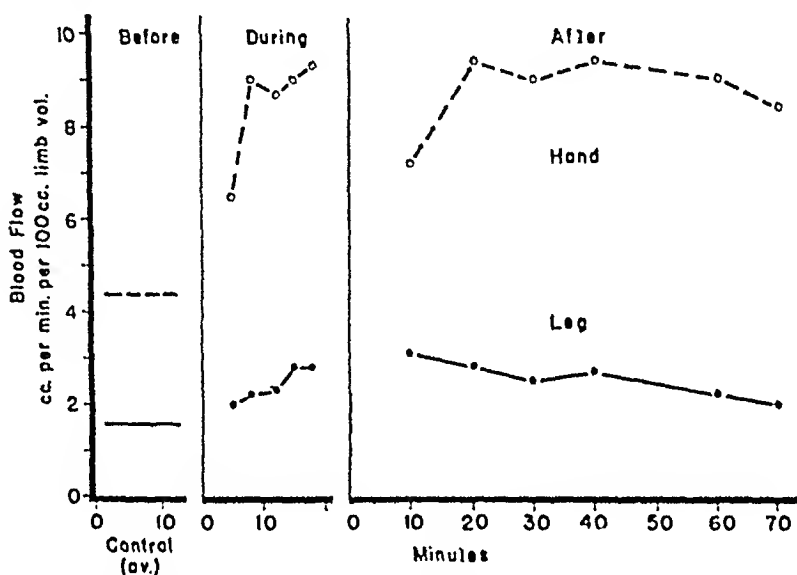


Fig. 2.—Effect of the intravenous injection of 250 c.c. of 5 per cent saline solution upon blood flow in the hand (dotted line) and leg (solid line).

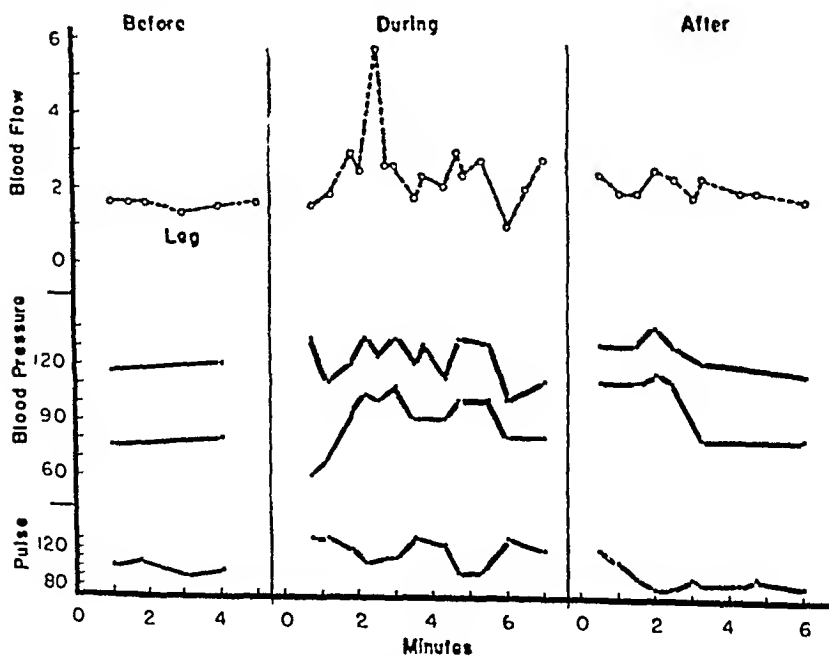


Fig. 3.—Effect of the intravenous injection of 0.35 mg. of histamine acid phosphate (dissolved in 10 c.c. of physiologic saline solution) upon blood flow in the leg, upon blood pressure, and upon pulse rate.

plethysmographic method. Linton, et al.,<sup>31</sup> who used the thermostromuhr in experiments on dogs, have recently reported that the flow does accelerate during this period.

#### DISCUSSION

It would seem from the data presented that most of the drugs which were studied did not consistently produce a significant and prolonged augmentation of the peripheral circulation. Alcohol, stilbestrol, and histamine increased the blood flow to the hand, but not elsewhere, and hypertonic saline solution had a similar effect on the leg and foot, as well as the hand, but only in about one-third of the trials. In respect to intermittent venous occlusion, no sustained state of reactive hyperemia appeared to be produced by the procedure—at least as far as could be ascertained by the plethysmographic method.

The fact that some investigators have used the skin temperature thermometer and the oscillogram in their studies may account in part for the different conclusions as to the vasodilator action of the various drugs. For example, Popkin,<sup>32</sup> who utilized both of these procedures, reported that nicotinic acid has either a slight effect, or none at all, upon peripheral blood flow. However, in a recent study<sup>12</sup> in which the plethysmographic method was used, it was found that this drug produced a significant and consistent increase in blood flow to the hand and forearm, although the skin temperature changes were similar to those reported by Popkin. Again, with massive doses of insulin,<sup>33</sup> very significant increases in blood flow to the forearm (four and five times the control level) were observed, whereas in some instances the forearm skin temperature actually fell during the period of accelerated blood flow. Of interest with respect to the relative value of the oscillogram is the case of a patient with multiple syphilitic aneurysms of the arch of the aorta which involved the orifices of the right innominate and left subclavian arteries.<sup>34</sup> The systolic blood pressure in both upper extremities was 40 to 50 mm. Hg, and the diastolic pressure could not be measured. As would be anticipated, the oscillogram readings, which depend upon the pulsatile change in the caliber of the large blood vessels, were reduced to 0.4 and 0.7 unit. Nevertheless, the blood flow to the hand and forearm at a bath temperature of 32° C. was normal; the readings were 12.0 c.c. and 1.1 c.c. per minute per 100 c.c. of limb volume, respectively. The skin temperature readings for the upper extremity were also within normal limits.

It would seem, then, that skin temperature measurements give little or no indication of changes in the circulation through the muscles. Further, the rather prevalent practice of using the finger tips and toes for investigating general responses in skin circulation is open to criticism because of the presence in these two areas of specialized blood vessels—the arteriovenous shunts. In respect to the oscillogram, the readings

are probably not modified significantly by blood flow through small collateral vessels, which, as Scott and Morton<sup>35</sup> have shown, play an important role in maintaining blood supply to the distal parts of a diseased limb. In view of these objections, it can be concluded that neither of these methods necessarily reflects total blood flow changes in an extremity.

At this point it must be stressed that all of the results herein reported were obtained following a *single* administration of the various drugs. We are well aware that many authors, using some of the procedures previously mentioned, have reported alleviation of symptoms only after a series of treatments. Hence, the fact that we did not observe an increase in peripheral blood flow with our method of study does not necessarily contradict their results. For, if a drug or a procedure is considered to have a beneficial effect because, in some as yet unexplained manner, it tends to increase collateral circulation after repeated trials, or because it stretches the venocapillary bed, as de Takats, et al.,<sup>36</sup> suggest is the reason for using intermittent venous occlusion, our observations cannot be utilized in its evaluation. On the other hand, if the drug or procedure is advocated for its immediate *vasodilating* action, it would be expected that this effect should be demonstrable even with a single administration.

#### SUMMARY AND CONCLUSIONS

By means of the venous occlusion plethysmographic method, the vasodilating action of a number of procedures used in the treatment of peripheral vascular disease was studied on a series of patients with peripheral circulatory impairment, on a series of patients with various mental states, and on a group of normal subjects.

It was found that, with a single administration, calcium gluconate, "Padutin," papaverin, "Spasmalgin," and thiamin chloride produced only a slight increase, or none at all, in the blood flow to the hand, forearm, leg, and foot. Alcohol, stilbestrol, and histamine generally increased the blood flow to the hand, but not to any other portions of the extremities. Hypertonic saline solution produced an augmentation of the flow to the hand, leg, and foot in only one-third of the trials. The intermittent application of a venous occlusion pressure for a period of two to three hours did not result in the production of a significant increase in peripheral blood flow.

Evidence was presented to indicate that the commonly employed clinical methods, namely, the skin temperature thermometer and the oscillogram, do not necessarily reflect or parallel changes in total blood flow to an extremity.

The authors wish to express their appreciation to Dr. S. Silbert and Dr. E. A. Baber for their help in supplying the patients used in this study, and to Dr. K. H. Katzenstein and Mrs. Robert Senior for their cooperation in carrying out the experiments.

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#### DISCUSSION

DR. BENJAMIN JABLONS, New York.—I believe that studies which are made with the plethysmograph should be accepted with a certain degree of reserve. We have made similar studies in evaluating therapeutic procedures in peripheral vascular disease, using methods which Dr. Abramson criticized, namely, surface and subcutaneous temperature measurements and oscillometry. We have come to some conclusions which are not entirely in agreement with those which Dr. Abramson has reported this morning.

For instance, we have studied the effect of nicotinic acid on some of our patients, and have found, in agreement with his report, that there is very little change in the surface temperature. There is, however, a marked drop in the muscle temperature. Also, there is a slight to moderate degree of diminution in the amplitude of the peripheral arterial pulsations, as determined by oscillometric recordings. Under the capillary microscope we have found that there is a narrowing of the arteriolar limb of the capillary, with a tendency to stasis in the venous limb of the capillary. Now, it must naturally be assumed that if there is stasis in the venous system as a result of the diminished *vis a tergo*, then the volume of the limb will naturally be increased. If, therefore, one takes the plethysmographic record as an index of blood flow, one is likely to assume erroneously that there is an increased flow of blood through the limb, when what occurs is merely an increased amount of fluid stagnant in that limb.

We, therefore, believe that the use of the oscillometer, which will indicate fluctuations in the amplitude of the arterial pulse, and surface temperature measurements, which indicate, of course, increased circulation through the capillaries, are much more likely to give the information that is valuable in determining the merit of various therapeutic procedures. I am in thorough agreement with Dr. Allen in regard to the value of surface temperature increases as an index of improvement in circulation when it is needed.



DR. NATHAN D. WILENSKY, Brooklyn, N. Y.—It is very obvious that the disagreement between the conclusions of Dr. Linton, which have just been presented, and those of Dr. Abramson on the effect of intermittent venous occlusion on arterial flow requires careful study in order to be comprehensible. Such divergent conclusions make it necessary to ascertain, first, whether the method employed for investigating the rate of arterial flow is reliable.

Several months ago Dr. Abramson published a paper in the AMERICAN HEART JOURNAL in which he demonstrated a large number of artifacts which appear in the tracings and create a situation which frequently may be interpreted as part of the physiologic phenomena, but, in reality, represents errors in plethysmographic technique.

In spite of the fact that this paper was devoted to the subject of artifacts, Dr. Abramson used certain criteria to interpret the effect of venous occlusion on the rate of arterial flow, and became an easy victim of artifacts which he used for physiologic interpretations.

In our own plethysmographic studies we found that the drop of the needle which follows immediately upon the release of the venous pressure is not the result of a decline in the volume of the limb below the control level, but is an artifact which we could produce at will.

This peculiar deviation from the observed plethysmographic studies of Lewis and Grant can easily be produced by applying the cuff in such a manner that the skin is pulled out of the boot. With proper support by means of sandbags, and by maintaining the knee flexed at an angle of 30°, this artifact can be avoided. Further evidence that this observation is a result of an error in technique can be found in Abramson's own studies, in which he demonstrated this phenomenon only in the lower extremity, but could not produce it in the upper extremity. I fail to understand this difference in observations, except in so far as it indicates that the technique in the lower extremity is more susceptible to error. In view of the fact that Abramson's studies produce different curves in the upper and lower extremities, one must be very careful about interpreting plethysmographic records in studying the constitutional effects of therapeutic agents on arterial flow.

It certainly appears that the thermostromuhr method which Linton employed is a much more accurate method for measuring absolute rate of flow through major vessels.

# VENOUS STASIS IN THE CORONARY CIRCULATION

## AN EXPERIMENTAL STUDY

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THE purpose of this article is to record data concerning stasis in the venous circulation of the heart. Any addition to the methods of treating coronary artery disease should be investigated. The available medical methods by drugs and rest are indirect. Perhaps a direct operative method can be evolved which will improve the vascular bed in the heart.

Ligation of a major vein and a major artery elsewhere in the circulatory tree has received considerable study. Both clinical and experimental observations support the conclusion that after a major artery to an extremity has been ligated the incidence of ischemic necrosis in the extremity is reduced by ligation also of the major vein. Surgeons accept this as a principle in surgery. According to Halsted, the idea originated with the Russian surgeon Von Oppel,<sup>1</sup> in 1908. On the basis of clinical observations Sir George Makins<sup>2, 4</sup> became an advocate of vein ligation with the artery. There are now considerable experimental data on this subject. Some of the experimental data are conflicting. In general, however, it appears that the incidence of necrosis is reduced by ligation of the vein with the artery. A brief résumé of this experimental work is given.

Brooks and Martin,<sup>5</sup> 1923, ligated the femoral artery in rabbits and found that the pressure distal to the ligation fell markedly in the arterial system and slightly in the venous system. When ligation of the femoral vein was added to this experiment, the venous pressure rose markedly and the arterial pressure also became higher. They found that 72.5 per cent of 21 animals developed necrosis of the leg after ligation of the artery and 33.3 per cent of 18 animals developed necrosis after ligation of both artery and vein. The conclusions by these experimenters were that simultaneous ligation of vein and artery (1) increased intravascular pressure in both arteries and veins, (2) decreased the volume flow of blood and (3) decreased the incidence of necrosis. It would appear, therefore, that a beneficial effect can be produced in the presence of a reduction in blood flow. Holman and Edwards,<sup>6</sup> 1927, found that the retrograde flow from the arterial stump distal to the ligation was increased by ligation of the vein. These experimenters concluded that ligation of the vein actually increased the flow distal to the arterial ligation. Brooks and Martin noted a reduction in temperature of the leg after ligation of the femoral artery and a further reduction in temperature when ligation of the vein was added to ligation of the artery. On this basis they concluded that blood flow was reduced by arterial ligation and still further reduced when ligation of vein was added to ligation of artery.

Theis,<sup>7</sup> 1928, made observations on the amount of blood flowing from the peripheral end of the ligated and divided femoral artery. He found that the retro-

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grade flow with artery alone ligated was less immediately than the retrograde flow with artery and vein ligated. The retrograde flow within an hour was the same in each type of experiment and three weeks later was greater in the arterial ligation than in ligation of both vein and artery. He assumed that the difference was explained by a better collateral circulation after ligation of the artery alone. However, this work is open to the criticism raised by Brooks that the flow of blood from the distal end of the divided artery did not represent the actual minute volume flow through the periphery of the limb. Furthermore, Theis found that the vascular bed, as determined by the roentgen appearance of the injected limbs, was greater immediately after ligation of the artery and vein; but that three weeks after ligation of the vessels, the vascular bed was more richly developed when the artery alone was ligated. This latter finding is in contradiction to that noted by Pearse,<sup>8</sup> 1927, that the vascular bed in the limb having the artery and vein ligated was much more abundant than that with the artery alone ligated, with the maximum degree of difference at the end of two weeks. Commenting on these observations, Brooks<sup>9</sup> stated that the size of the blood vessels as determined by injection was not a reliable index of the actual volume flow through the tissues and that the condition of the vascular tree three weeks after a sudden arterial occlusion was not necessarily important in the study of the cause of gangrene. He claimed that venous ligation was only of temporary benefit. Mulvihill, Harvey, and Doroszka,<sup>10</sup> 1931, in experiments on 7 dogs ligated the external iliac artery and vein in one extremity and the artery alone in the other extremity. Gangrene did not develop in either extremity. The temperature curves were identical on both sides. They found that the temperature dropped gradually to room temperature in each leg over a period of three hours. The temperature remained at that point for about three hours. Then it suddenly rose to normal body temperature where it remained. The greater part of this sudden rise in temperature took place in a period of twenty minutes. Mulvihill and his co-workers believed that this sudden rise signified the establishment of collateral circulation by means of a vasomotor mechanism. They concluded that simultaneous ligation of the vein had no demonstrable effect in aiding or retarding the development of collateral circulation. Montgomery,<sup>11</sup> 1932, noted that following ligation of the femoral artery the peripheral arterial and venous pressures rose when the vein was ligated, whether the latter was the superficial femoral, the iliac, the common iliac or the inferior vena cava. In general, the peripheral pressures became higher as the ligature was placed nearer to the heart. However, the volume flow was progressively decreased by placing the ligature nearer to the heart. Montgomery agreed with Brooks that the beneficial effects of venous ligation were not due to an increase in blood flow, but that the ligation of the vein re-established the reduced peripheral blood pressures to a level above the minimum necessary to maintain a sufficient distribution of blood throughout the venous capillary bed and preserved the head of pressure required for the passage of nutrient elements from the capillaries into the surrounding tissues.

ligation than after arterial and venous ligation. Contractures developed in 15 animals in which the arteries alone were ligated and in only 4 animals in which both arteries and veins were ligated. The difference between the two groups was more striking if the mortality rate was considered: 58 per cent of the animals lived five days or more with the artery alone ligated, while 70 per cent of the animals lived five days or more with the artery and vein ligated. Brooks and his co-workers stated that gangrene and necrosis were the immediate and direct effects of deficient blood flow; that contractures were the result of the process of repair and were evidence of a previous impairment of circulation sufficiently great to produce necrosis of vulnerable tissue. The decreased incidence of contractures after vein ligation demonstrated the preservation of vitality of the more vulnerable tissue during critical periods before the reestablishment of circulation through the collateral vessels.

Similar studies on the veins and arteries of the hearts of dogs were carried out by Gross, Blum, and Silverman.<sup>13</sup> With complete occlusion by ligation or other methods (escharotics, etc.) of the coronary sinus where it entered the right atrium, they obtained a mortality rate of 42 per cent (37 out of 89 dogs), occurring in the first twenty-four hours after ligation. Partial occlusion of the coronary sinus, however, carried a mortality rate of 10 per cent (4 out of 39 dogs). Unsuccessful occlusion of the coronary sinus produced a mortality rate of 21 per cent (6 out of 29 dogs). As a control series, ligation of the descending ramus of the left coronary artery, performed at a point 2 cm. from the ostium of the circumflex artery, resulted in a mortality rate of 53 per cent (28 out of 53 dogs), occurring within twenty-four hours after ligation. Of the 25 dogs that survived all showed infarcts of the heart, and in 24 of these the infarcts were invariably of uniform size and large filling defects of the coronary tree were noted on injection with barium gelatin. Ligation of the descending ramus at the same location, one to eight weeks (average four weeks) after complete occlusion of the coronary sinus yielded a mortality rate of 55 per cent (16 out of 29 dogs) or the same as the mortality rate among the animals of the controls. Of the 13 dogs surviving the above procedure, 7 showed no infarcts and in the other 6 dogs all the infarcts were considerably smaller than the infarcts found in the controls. In these hearts in which both artery and vein were ligated, the vascular tree was increased in extent and the filling defects on injection were either absent or small. Ligation of the descending ramus one to six weeks after partial occlusion of the coronary sinus resulted in a mortality rate of 31 per cent (9 out of 29 dogs). Of the 20 dogs surviving in the above experiments, 2 of the hearts showed no infarcts, 9 had infarcts much smaller than those of the controls, and 9 had infarcts of the same size as the hearts of the controls.

Gross and his co-workers claimed that coronary sinus occlusion produced an extensive and abundant dilatation of the intramyocardial collateral channels and the success of the procedure, discounting the mortality rate, depended upon the completeness of the coronary sinus occlusion. However, sudden and complete occlusion of the coronary sinus by itself was associated with a high operative mortality (42 per cent) and complete occlusion of the sinus did not change the mortality rate after ligation of the artery. Partial occlusion of the sinus by itself had a lower operative mortality and also lowered the mortality rate when ligation of the descending coronary artery was done subsequently. The infarcts obtained in the dogs with partial occlusion of the sinus were smaller than those obtained without any obstruction of the sinus but they were not as small as those obtained after complete obstruction of the sinus. Gross and his coworkers concluded that "complete or even partial occlusion of the coronary sinus, whether this be permanent or transient, affords a definite method of anatomically and functionally enriching the coronary bed to such an extent that infarction may be either completely prevented

or minimized." Thus, they base their enthusiastic conclusions of the beneficial effects of sinus ligation on the presence and size of infarcts, stating that the mortality rate was unaffected except in partial sinus occlusion.

Katz, Jochim, and Bohning<sup>14</sup> found that occlusion of the coronary sinus resulted in a decrease in the total coronary artery inflow. These authors concluded that there was no rationale to ligation of the coronary sinus as a method to increase the coronary arterial bed.

Gregg and Dewald<sup>15,17</sup> carried out physiologic studies after ligation of coronary vessels. They found that the pressure in the coronary sinus rose to the level of aortic pressure after the sinus was ligated. They found the contour and time relations of the venous pressure curves to resemble closely the curves obtained from the coronary artery. They also found that the pressure in the peripheral coronary arterial bed was increased by ligation of the coronary sinus. The inflow into the left coronary artery was significantly reduced by sinus ligation. They ligated the left descending coronary artery and coronary sinus and found that the systolic pressure in the artery peripheral to the ligature was approximately equal to or even higher than the aortic systolic pressure. They stated that this pressure had its source largely in other nonoccluded arteries. Also, the more proximal the ligation of the vein to the sinus, the higher was the peripheral coronary pressure. The retrograde blood flow from the left descending coronary artery was markedly elevated after the coronary sinus was ligated. When the artery was ligated and cut, the retrograde flow was about 1 c.c. per minute. After ligation of the coronary sinus the retrograde flow from the artery was as high as 39 c.c. per minute; the maximum peripheral flow was reached in from ten to thirty minutes and did not immediately return to control backflow figures following release of the ligature around the sinus. This value of 39 c.c. per minute approaches or equals the volume of blood which might be expected to flow into the central nonoccluded coronary artery. The retrograde blood was highly unsaturated, containing only 3 to 4 volumes per cent oxygen. The oxygen content of blood drawn from the coronary sinus under normal conditions was 8 volumes per cent. They found that the myocardium failed to contract over the area supplied by the ligated artery. They also found that occlusion of the sinus had practically no effect on the circulation in the right side of the heart. Gregg and Dewald do not believe that venous ligation is a method of "choice" for encouraging the blood supply to a potentially in-

Fauteux,<sup>20</sup> of Montreal, ligated the magna cordis vein and the descending ramus of the left coronary artery. He concluded from his experiments that ligation of this vein reduced the mortality that follows ligation of the artery alone. Fauteux was eager to ligate this vein in patients with sclerosis of the descending ramus of the left coronary artery and recently carried out this operation.

#### ADDITIONAL EXPERIMENTS ON LIGATION OF CORONARY ARTERY AND VEIN

We carried out experiments on this subject for the purpose of obtaining the answer to two questions: (1) whether ligation of coronary veins reduced the mortality after ligation of an artery and (2) whether ligation of veins brought about a reduction in the size of the infarct. The artery selected for our study was the descending ramus of the left coronary artery just below the bifurcation of this artery (Fig. 1). The veins ligated were either the coronary sinus where it entered the right atrium (Fig. 2) or the magna cordis vein where it lay beneath the left auricle (Fig. 3). In some of the experiments the veins from the right ventricle were ligated as they entered the right atrium, thus producing stasis in almost the entire venous system of the ventricles.

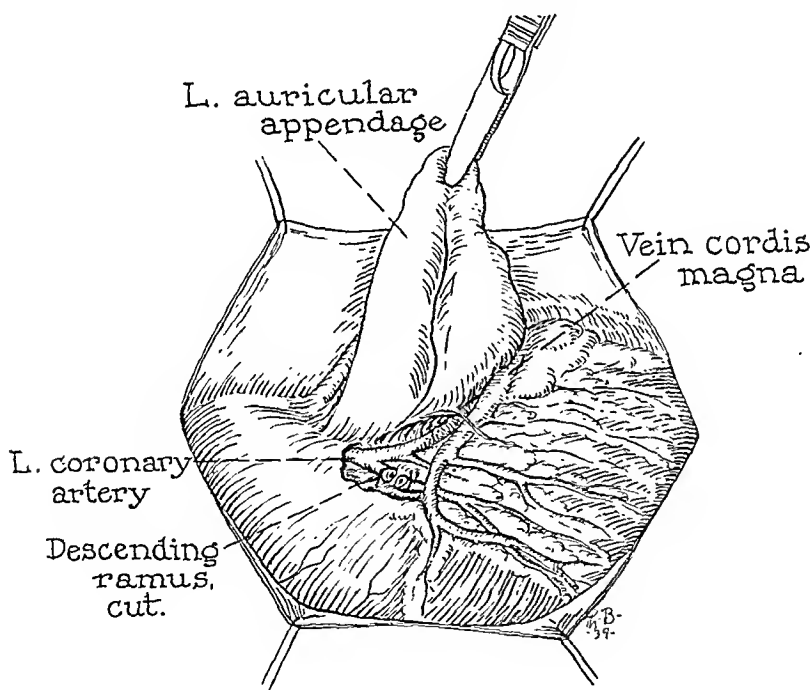


Fig. 1.—The left coronary artery was exposed at its bifurcation into the ramus descendens and the ramus circumflexus. The ramus descendens was isolated, doubly ligated, and cut between ligatures. The level for ligation was always here, never at a variable point along the artery.

*Ligation of Coronary Veins.*—Ligation of the coronary veins is followed by slowing of the heart rate, cyanosis of the ventricles, distention of veins, and enlargement of the heart. These observations were also made by Gross and his co-workers. The mortality rate following complete ligation of the coronary sinus in our hands was about 2 per cent. Gross, Blum, and Silverman reported a mortality of 42 per cent follow-

ing ligation of the coronary sinus. This great difference in mortality can be accounted for only on the basis of surgical technique, mechanical respiration, anesthesia, and avoidable complications to operation.

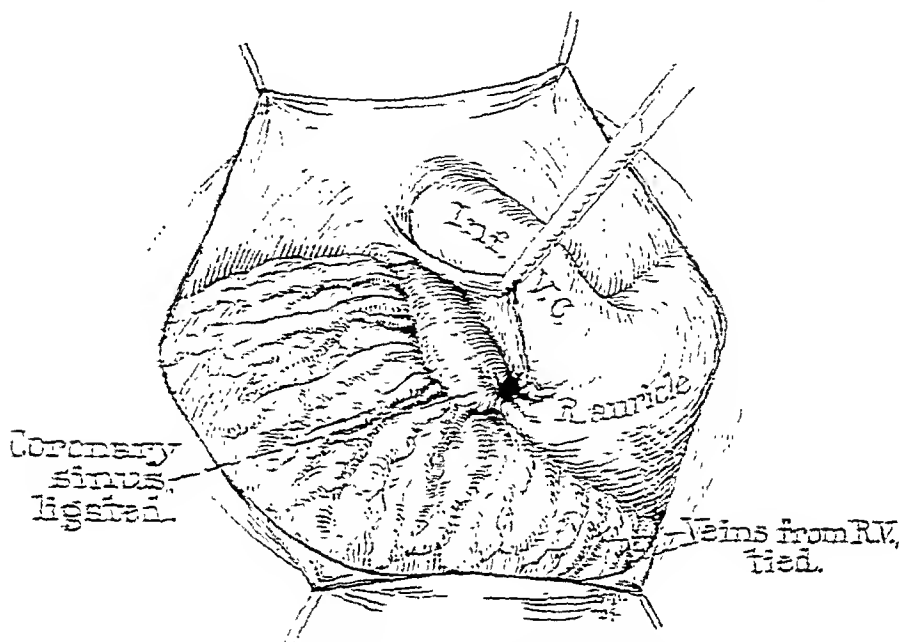


Fig. 2.—The coronary sinus was dissected and ligated with silk.

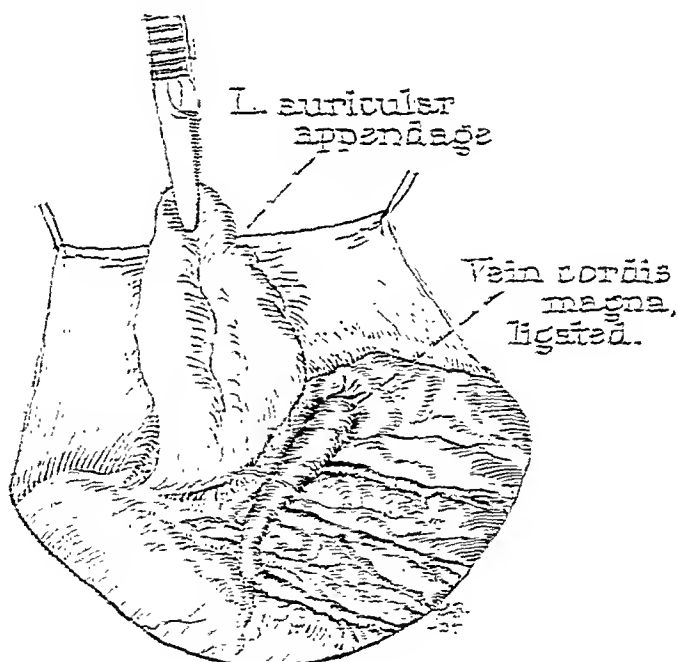


Fig. 3.—Ligation of magna cordis vein.

*Ligation of Coronary Artery.*—The left coronary artery was dissected at its bifurcation. The descending ramus was doubly ligated and cut immediately below its bifurcation. Every care was taken to avoid all factors that might increase the mortality rate. Three series of 10 dogs each were done at widely spaced intervals of time. The mortality

was 9, 8, and 7, or a total of 24 in 30, a mortality rate of 80 per cent (Table I). Seven or 29 per cent died within five to thirty minutes after

TABLE I  
LIGATION OF DESCENDING RAMUS OF LEFT CORONARY ARTERY

NUMBER OF DOGS	DIED	SURVIVED	MORTALITY RATE
10	9	1	90%
10	8	2	80%
10	7	3	70%
Total 30	24	6	80%

ligation; 15 or 63 per cent died within two to eighteen hours; one died fifteen days, and another eighteen days, after ligation. Complete autopsy failed to reveal any other cause of death in these last two dogs so that the cause of death must be ascribed to the ligation of the artery. These two dogs had infarcts which were among the smallest that were observed in the series of control experiments. Nothing that could be considered as infarcts was present in the dogs that died within eighteen hours except for questionable color changes of the myocardium. These color changes on microscopie examination failed to reveal any variation from the normal appearance of heart muscle. The six dogs that recovered were observed over a period of twelve days to eight months; the dog living twelve days was killed because of severe distemper; the remainder were killed from five weeks to eight months after ligation of the artery.

*Ligation of Coronary Vein and Artery.*—The first series consisted of 10 dogs. The artery was dissected. The magna cordis vein was ligated. Within a few minutes after ligation of this vein the artery was ligated and cut. Three of these dogs lived and 7 died (5 of which died from five to thirty minutes after ligation); mortality rate 70 per cent. The second series consisted of 10 dogs. In this series the coronary sinus was ligated and after an interval of three to six days (average 3.8 days) a second operation was done and the artery was ligated and cut. Two of these dogs lived and 8 died (five of which died from five to thirty minutes after ligation); mortality 80 per cent. The third series consisted of 10 dogs. In this series the coronary sinus was ligated and after an interval of seven to seventeen days (average thirteen days) a second operation was done and the artery was ligated and cut. Five of these dogs lived and 5 died (2 of which died from five to thirty minutes after ligation, 1 about eighteen hours later, 1 about thirty-six hours later, 1 about five days later); mortality 50 per cent. The fourth series consisted of 10 dogs. In this series the magna cordis vein was ligated and after an interval of six weeks a second operation was done and the artery was ligated and cut. Five of these dogs lived and 5 died (4 of which died five to thirty minutes after ligation); mortality 50 per cent. The fifth series consisted of 17 dogs. In this series the coronary sinus was ligated and after an interval of four months a second operation was done and the



artery was ligated and cut. Seven of these dogs lived and 10 died (5 of which died five to thirty minutes after ligation, 4 at the end of eighteen hours and 1 in twenty-nine hours); mortality 59 per cent (Table II).

TABLE II

LIGATION OF VEIN AND LIGATION OF DESCENDING RAMUS OF LEFT CORONARY ARTERY

SERIES	NUMBER OF DOGS	VEIN LIGATED	INTERVAL BETWEEN LIGATION OF VEIN AND LIGATION OF ARTERY	DIED	SURVIVED	MORTALITY RATE
I	10	Magna Cordis	At same operation	7	2 killed, 10 months 1 killed, 8 days, distemper	70%
II	10	Coronary Sinus	3 to 6 days Average 3.8 days	8	2 killed, 2 months	80%
III	10	Coronary Sinus	7 to 17 days Average 13 days	5	2 killed, 4 weeks 2 killed, 3 weeks 1 killed, 2 weeks	50%
IV	10	Magna Cordis	6 weeks	5	4 killed, 8 months 1 killed, 3 months	50%
V	17	Coronary Sinus	4 months	10	7 killed, 3 months	59%
Total	57			35	22	61%

It was found that many animals died from ventricular fibrillation five to thirty minutes after ligation of the artery. If the animal survived this early period it usually lived several hours and was found dead in the cage the next morning. The deaths can be grouped as immediate and delayed. In the control group death was immediate, i.e., within thirty minutes, in 29 per cent and delayed in 71 per cent. In the entire group in which vein and artery were ligated, death was immediate in 60 per cent and delayed in 40 per cent.

At the time of re-operation for ligation of the artery, the heart itself presented a variable picture. The degree of venous engorgement varied widely in the same series. Three to six days after occlusion of the coronary sinus, the heart was usually enlarged due to venous engorgement and the contractions were somewhat sluggish. The veins, even minute ones, were distended. They were easily torn and bled freely. In some experiments hemostasis was difficult to obtain because of the elevated venous pressure. Two weeks after venous ligation the engorgement of veins and the distention of the heart were less marked and the heartbeat appeared to be stronger. Six weeks after ligation of the magna cordis vein the distention of the veins was still observed but it was slight. At four months distention of veins was not observed. We found definite evidence of fibrosis in the fat around the coronary artery. This was observed in our dissection of the artery and was found in practically all hearts in which venous stasis had been produced. It can be mentioned

here that Brooks and his co-workers noted fibrosis in their experiments on the extremities. However, the fibrosis was not found in the heart muscle either grossly or microscopically.

*Analysis of Infarcts.*—Difficulty was encountered in making measurements of the infarcts. The infarct could not be measured before degenerative changes had sufficient time to take place. An infarct of less than twenty-four hours' duration showed only macroscopic color change in the myocardium. Under the microscope the heart muscle appeared normal, as a rule, up to twenty or twenty-four hours. Necrosis, separation of muscle bundles, and poor staining affinity then appeared. Later on the infarct became a cicatrix. The extent of the cicatrix was variable. In some specimens the septum was slightly involved; in others the cicatrix extended across the entire septum. The thickness of the cicatrix was variable. In some specimens it extended across the entire thickness of the ventricular wall; in other specimens it involved only part of the wall.

We observed these infarcts as closely as we could and we can say that the cicatrices obtained in the control experiments were about the same size as those obtained in experiments after vein and artery ligation. The specimens in the third series of vein and artery ligation with an interval of seven to seventeen days and with a 50 per cent mortality showed infarcts that were slightly smaller than the infarcts of the controls. In the other series the difference, if any, was so slight that we could not recognize it.

It was thought that injection of the coronary arteries with barium gelatin might be of some value in determining the size of the intercoronary communications. The technique of the injection was identical in all hearts and one technician injected all specimens. The circumflex branch of the left coronary artery and the right coronary artery were injected. The injection mass that entered the descending ramus of the left coronary artery did so by way of intercoronary communications with the two injected arteries. It was seen that there was good filling of the distal portions of the left descending coronary artery in every heart that survived ligation of the artery, whether the vein was or was not ligated also. This occurred because communications with the right and with the left circumflex arteries developed. This development of intercoronary communications is an important compensation for coronary artery obstruction in the dog. In these hearts that survived arterial ligation, most of the infarcts showed a moderate number of injected arteries even in areas of marked scarring. In an analysis of 22 hearts in which the artery only was ligated, 50 per cent had good filling of the descending ramus, 10 per cent had poor filling and 40 per cent had no filling of the artery. In an analysis of 54 specimens in which vein and artery were ligated, 76 per cent showed good filling, 13 per cent had

poor filling and 11 per cent showed no filling of the distal end of the descending ramus of the left coronary artery. It appears then that venous ligation has a tendency to open intercoronary communications. However, this was not sufficient to prevent the development of an infarct in a single experiment.

*Partial Occlusion of Coronary Artery.*—We carried out experiments in which the descending ramus of the left coronary artery was partially and not completely occluded. The purpose was to increase the survival rate so that a larger number of specimens were available for study. We recognize that this procedure adds a variable factor to the experiment. Eleven pairs of dogs were selected. Each pair was about the same size and weight. The descending ramus was dissected at the bifurcation of the left coronary artery as in the other experiments. In one of each pair the magna cordis vein was ligated well around the left posterior aspect of the heart about 3 cm. from the coronary sinns. To do this the heart was rotated. After this ligation was made, a ligature was placed around the artery and tied to include with the artery a metal stilette about one millimeter in diameter. The stilette was then removed. However, it was quite impossible to produce the same degree of occlusion in each pair of dogs. When the hearts were examined we found that our tendency had been to give a greater degree of occlusion to the experiment involving both vein and artery, as compared to the experiment with artery alone. The results are given in Tables III and IV. These dogs were killed three months after operation.

TABLE III

## PARTIAL OCCLUSION OF DESCENDING RAMUS OF LEFT CORONARY ARTERY

EXPERIMENT	LIVED	DIED	MYOCARDIUM	APPROXIMATE DEGREE OF ARTERIAL OCCLUSION
1	+		No infarct	90%
2	+		Large infarct	100%
3	+		Small infarct	75%
4	+		No infarct	75%
5		12 hours	Too early to show infarct	75%
6	+		No infarct	95%
7		12 hours	Too early to show infarct	95%
8		14 days	No infarct	80%
9	+		No infarct	85%
10	+		Infarct of medium size	90%
11		3 hours	Too early to show infarct	90%

In the control group with ligation of artery alone 4 died and 7 recovered. The mortality rate with the artery alone was 36 per cent and the degree of occlusion as estimated by observation was 86 per cent. One specimen in this group showed complete occlusion. The mortality rate with vein and artery ligated was 18 per cent and the degree of occlusion as estimated by observation was 95 per cent. Five specimens in this group showed complete occlusion. Halsted in his work on blood vessel

TABLE IV

LIGATION OF MAGNA CORDIS VEIN AND PARTIAL OCCLUSION OF DESCENDING RAMUS OF LEFT CORONARY ARTERY

EXPERIMENT	LIVED	DIED	MYOCARDIUM	APPROXIMATE DEGREE OF ARTERIAL OCCLUSION
1	+		Focal areas of fibrosis only	100%
2	+	12 hours	No infaret	95%
3	+		Too early to show infaret	100%
4	+		No infaret	90%
5	+		Small infaret with focal areas of fibrosis	100%
6	+	12 hours	No infaret	95%
7	+		No infaret	90%
8	+		Too early to show infaret	100%
9	+		No infaret	80%
10	+		Medium size infaret	100%
11	+		Medium size infaret	95%

surgery showed that a ligature that almost completely occluded an artery when it was applied could become completely occlusive after a cicatrix formed around the ligature. It is our opinion that this occurred in these experiments. Three specimens with complete occlusion of the artery and vein showed infarets that were smaller than any infaret produced by complete arterial occlusion either in this series or in the other series of 30 control experiments. The specimens with vein ligation plus partial arterial ligation showed less destruction of the myocardium than did the specimens with partial arterial ligation alone.

## DISCUSSION AND CONCLUSIONS

Does ligation of the vein reduce the mortality rate following ligation of a coronary artery? The answer to this question was difficult to ascertain and we had to carry out many experiments to obtain sufficient data. We had to use 30 dogs to get a standard for comparison. A considerable variation existed in the mortality of this group. The total mortality for complete occlusion of the artery was 80 per cent, 24 out of 30. Likewise, a considerable variation existed in the mortality following occlusions of vein and artery. The total mortality was 61 per cent, 35 out of 57. A glance at the experiments in the latter group shows that the mortality was not reduced in the series in which ligation of the vein was followed by ligation of the artery at the same operation or after an interval of three to six days. Perhaps the two operations in succession should be given some consideration in the mortality but this we cannot evaluate. The figures indicate that the mortality is reduced if a period of seven days to four months intervenes between ligation of vein and ligation of artery. In these groups the mortality was 50 per cent, whereas, the lowest mortality in any of the three control series of 10 each was 70 per cent.

More conclusive results were obtained in the experiments with partial ligation of the artery. In this group the mortality was lower and the degree of occlusion was greater than with venous ligation plus partial occlusion of the artery. A larger number of dogs survived a greater degree of arterial occlusion in the group in which ligation of the vein was added to the occlusion of the artery.

Does ligation of the vein reduce the size of the infarct? In the experiments in which the artery was completely occluded we could see no definite difference in the size of the infarct whether the vein was or was not occluded. A possible exception to this statement was in the third series in which the infarcts were slightly smaller than were those of the control group. In the experiments with partial ligation of the artery, the difference in the size of the infarcts was definite. In these experiments it appears that ligation of the vein does reduce the size of the infarct as compared to the infarct following partial occlusion of the artery only. The infarcts in this group of experiments with ligation of the vein plus partial occlusion of the artery were smaller than the infarcts with partial and less marked occlusion of the artery only.

Finally, we are confronted with the question of application of this work in the treatment of occlusion of the coronary arteries. Do the experiments show sufficient beneficial effect to indicate ligation of the coronary sinus or magna cordis vein in the human heart for the purpose of improving the coronary circulation in patients with coronary sclerosis? Our feeling about this is that the beneficial effect probably is not great enough to justify application. We would like to suggest that further measurements be made before considering this as a therapeutic procedure.

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# THE SIGNIFICANCE OF DIAGNOSTIC TESTS IN THE STUDY OF PERIPHERAL VASCULAR DISEASE

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**D**URING the past few years numerous methods for estimating the degree and distribution of peripheral arterial occlusion and vasoconstriction have been described. These methods have added greatly to our clinical knowledge of vascular diseases such as arteriosclerosis obliterans, thromboangiitis obliterans, various vasospastic conditions, and numerous less common peripheral vascular disorders. They are aids in diagnosis and prognosis and help indicate appropriate therapy. In the past seven years 1,027 patients have been studied in the Peripheral Vascular Clinic of the Hospital of the University of Pennsylvania. Only 75 per cent of this number were found to have peripheral vascular disease (Table I). The present communication is presented in order to show the usefulness of diagnostic tests in evaluating the circulatory disorder from the standpoint of prognosis and treatment (Table II).

Frequently the tests served to confirm pathologic and functional diagnoses based on history and physical examination, usually they gave some additional information, and not uncommonly they changed the diagnosis. In a series of seventy-one consecutive cases of peripheral arteriosclerosis, thromboangiitis obliterans, or abnormal vasoconstriction (Table III), the diagnosis which was made from the history and physical examination was confirmed by diagnostic tests in 53 per cent, was amplified ("functional diagnosis") in 30 per cent, and was refuted in 17 per cent. Accuracy of prognosis was generally improved as a result of employing the diagnostic tests, although the remittent character of the disease in many cases determined the ultimate outcome.

Vasodilatation tests gave the most reliable information. Frequently they were used to substantiate the clinical impression formed from the history and physical examination, and in such instances they established the diagnosis more firmly on a physiologic basis. In those cases in which the tests were functionally diagnostic the immediate prognosis was established. In no case was misleading information gained from properly performed tests. A list of the tests is given in Table IV.

## ELEVATION AND DEPENDENCE OF LIMBS

Several tests are a part of the routine examination of patients who are suspected of having peripheral arterial disease. The simplest of these is

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TABLE I

DIAGNOSES OF ALL PATIENTS SEEN IN THE PERIPHERAL VASCULAR CLINIC  
1933-1940\*

"STRICTLY" PERIPHERAL VASCULAR DISEASE DIAGNOSES	
1. Arteriosclerosis—without diabetes	252
2. Arteriosclerosis—with diabetes	94
3. Thromboangiitis obliterans	121
4. Abnormal vasoconstriction (a) Raynaud's disease	19
(b) other	
5. Varicose veins	36
6. Thrombophlebitis (a) acute	16
(b) chronic	7
7. Embolism	16
8. Acrocyanosis	13
9. Scleroderma	11
10. Lymphedema	9
11. Varicose ulcer	9
12. Erythromelalgia	5
13. Scalenus anticus syndrome	4
14. Congenital arteriovenous fistula	3
15. Cervical rib	2
16. Sensitivity to tobacco	2
17. Thrombosis saphenous vein	2
18. Recurrent lymphangitis (idiopathic)	2
19. Femoral artery thrombosis of unknown origin	2
20. Recurrent phlebitis of unknown origin	2
21. Traumatic aneurysm femoral artery	1
22. Traumatic arterial occlusion (by cast)	1
23. Traumatic arterial spasm	1
24. Thrombosis? of abdominal aorta	1
25. Axillary artery thrombosis, cause unknown	1
26. Traumatic vasospasm (pneumatic hammer)	1
27. Oil embolus (bismuth in oil)	1
28. Traumatic arteriovenous aneurysm	1
29. Thrombosis common iliac veins	1
30. Axillary vein thrombosis	1
	722
OTHER PERIPHERAL VASCULAR DISEASES	
1. Cerebral vascular, symptoms in extremities	10
2. Frostbite of digits	6
3. Hypothyroidism—coldness in extremities	3
4. Polycythemia vera—erythromelalgic symptoms	2
5. Localized scleroderma—morphea	2
6. Poliomyelitis	1
7. Edema of unknown origin	1
8. Postoperative carcinoma of breast	1
9. Injury to lymphatics with obstruction	1
10. Stump edema—poor lymphatic return	1
11. Thrombosis of central retinal artery	1
12. Surgically induced hypotension	1
13. Arteriosclerosis of spinal cord	1
14. Arterial spasm secondary to coronary artery disease	1
15. Causalgia	1
	33

\*Final diagnoses in 1,027 cases from the Peripheral Vascular Clinic of the Hospital of the University of Pennsylvania.



ENTIRELY NONVASCULAR DIAGNOSES MADE IN THE PERIPHERAL  
VASCULAR CLINIC

1. Hypertrophic arthritis	28
2. Pes Planus	16
3. Neurosis	13
4. Peripheral neuritis in diabetic patients	10
5. Peripheral neuritis in nondiabetic patients	10
6. Dermatophytosis (primary cause of symptoms)	9
7. Atrophic arthritis	6
8. Obesity	6
9. Menopausal paresthesias	6
10. Referred for studies of sympathetic system	6
11. Traumatic neuritis—cast, trauma	5
12. Sprained ankle	4
13. Sciatica	3
14. Low blood chlorides	3
15. Erysipeloid of leg—dermatophytosis?	3
16. Shortening of tendon Achilles	2
17. Temporary neuritis caused by salicylic acid	2
18. Syphilis	2
19. Meralgia paresthetica	2
20. Traumatic gangrene—nonvascular	2
21. Neurologic lesions	
chronic sclerosing myelitis	1
posterolateral sclerosis	1
myelitis anesthesia	1
Parkinsonism	1
amyotrophic lateral sclerosis	1
Charcot-Marie-Tooth disease	1
spastic paraplegia	1
progressive unilateral hemiatrophy	1
22. Intestinal malignancy	1
23. Gout	1
24. Hyperhidrosis	1
25. Infection of toe—nonvascular	1
26. Nonvascular ulcer on leg—traumatic	1
27. Fracture of metatarsals	1
28. Spondylolisthesis of lumbar vertebra	1
29. Neuritis of pregnancy	1
30. Club feet	1
31. Sprain fracture, external malleolus	1
32. Bursitis of popliteal space	1
33. Disuse atrophy	1
34. Nutritional edema	1
35. Pernicious anemia	1
36. Improper shoes	1
37. Herpes zoster	1
38. Hyperpituitarism	1
39. Congenital band around leg	1
40. Calcium deficiency	1
41. Old osteomyelitis	1
42. Bursitis (subacromial)	1
43. Myositis	1
	168
Diabetes without peripheral arterial disease	31
Diseases with symptoms in extremities not diagnosed in the Peripheral Vascular Clinic	73
Total number of patients examined	1027

observation of the effect of position on skin color. While the patient reclines, the legs are raised and the degree and rate of blanching of the feet are noted. Normally, blanching is incomplete and slow; but blanching is complete within several seconds when many arteries are occluded. The patient then sits up and places the feet on the floor. If the subject



TABLE III  
CLINICAL VALUE OF TESTS

SEX	AGE	PERIPH. ARTERIAL DIAG., PATH. AND FUNCTIONAL		VALUE OF TESTS	FOLLOW-UP
		FROM HIST. AND PHYS. EXAM.	FROM HIST., P. EX. AND TESTS		
No Peripheral Vascular Disease					
F	57	?Arterioscl.	No P.V. disease	Diagnostic	5 yr. No P.V.D.
F	46	No per. vas. disease	No P.V.D.	Confirmatory	2 yr. No P.V.D.
F	36	?Per. vas. disease	No P.V.D.	Diagnostic	2 yr. No P.V.D.
M	38	No per. vas. disease	No P.V.D.	Confirmatory	2 yr. No P.V.D.
M	55	Diabetes, ulcer, no P.V.D.	No P.V.D.	Confirmatory	2 yr. No P.V.D.
F	23	No per. vas. dis.	No P.V.D.	Confirmatory	2 yr. No P.V.D.
Arteriosclerosis With Occlusion					
M	63	Arterioscl. ? severity	Arterioscl. good collat.	Funct. diag.	5 yr. Asympt.
M	65	Abnormal vasoconst.	Arterioscl. good collat.	Diagnostic	2 yr. Arteriosc.
F	66	Arterioscl. moderate	Arterioscl. good collat.	Confirmatory	7 yr. moderate
M	68	Arterioscl. severe	Arterioscl. severe	Confirmatory	2 yr. Asympt.
M	54	Arterioscl., ? grade	Arterioscl. good collat.	Funct. diag.	3 yr. Asympt.
M	75	Arterioscl. mod. severe	Arterioscl. good collat.	Funct. diag.	3 yr. Asympt.
M	58	Arterioscl. severe	Arterioscl. good collat.	Funct. diag.	5 yr. Asympt.
M	53	Arterioscl. gangrene	Arterioscl. fair collat.	Funct. diag.	5 yr. Asympt.
M	57	Arterioscl. severe	Arterioscl. fair collat.	Funct. diag.	2 yr. Asympt.
F	70	Arterioscl. slight	Arterioscl. slight	Confirmatory	4 yr. Asympt.
M	56	Arterioscl. ? degree	Arterioscl. moderate	Funct. diag.	2 yr. Asympt.
M	70	?Arteriosclerosis	Arterioscl. severe	Diagnostic	2 yr. no change
M	80	Arterioscl. severe	Arterioscl. poor collat.	Confirmatory	3 yr. Asympt.
M	63	Arterioscl. moderate	Arterioscl. good collat.	Confirmatory	3 yr. Inter. Cla.
Diabetic Arteriosclerosis With Occlusion					
M	46	Arterioscl. severe	Arterioscl. severe	Confirmatory	8 yr. Asympt.
F	51	Arterioscl. severe	Arterioscl. good collat.	Funct. diag.	3 yr. Asympt.
M	82	Arterioscl. severe	Arterioscl. fair collat.	Funct. diag.	5 yr. Asympt.
F	56	Arterioscl. moderate	Arterioscl. poor collat.	Funct. diag.	5 yr. Asympt.
F	60	Arterioscl. severe	Arterioscl. fair collat.	Funct. diag.	5 yr. Asympt.
M	62	Arterioscl. moderate	Arterioscl. rather severe	Confirmatory	2 yr. Asympt.
F	46	Arterioscl. moderate	Arterioscl. good collat.	Confirmatory	2 yr. Improved
M	57	Arterioscl. severe	Arterioscl. severe	Confirmatory	2 yr. Improved
M	46	?Arterioscl.	Arterioscl. spastic element	Diagnostic	3 yr. Asympt.
M	56	Arterioscl. ? grade	Arterioscl. mod. collat.	Funct. diag.	4 yr. Improved
M	56	Arterioscl. severe	Arterioscl. fair collat.	Funct. diag.	5 yr. Asympt.
F	54	Arterioscl. severe	Arterioscl. severe	Confirmatory	2 yr. no change
M	58	Arterioscl. moderate	Arterioscl. moderate	Confirmatory	2 yr. no change
F	61	Arterioscl. severe	Arterioscl. good collat.	Funct. diag.	2 yr. Imp., Fail.
F	45	?Arterioscl.	Arteriosclerosis, mild	Diagnostic	3 yr. Improved
F	54	Arterioscl. moderate	Arterioscl. fair collat.	Confirmatory	2 yr. Improved

*Thromboangitis Obliterans*

M	34	T.A.O. severe	T.A.O. good collat.	Funct. diag.	2 yr. no change
M	25	T.A.O. severe	T.A.O. slight collat.	Confirmatory	3 yr. healing
M	35	T.A.O. severe	T.A.O. good collat.	Funct. diag.	3 yr. healed
M	33	T.A.O. severe	T.A.O. some collat.	Confirmatory	2 yr. just healed
M	28	T.A.O. severe	T.A.O. negligible collat.	Confirmatory	6 yr. recur. ulc.
M	37	T.A.O. severe	T.A.O. slight collat.	Confirmatory	5 yr. recur.
M	41	T.A.O. severe	T.A.O. negligible collat.	Confirmatory	4 yr. Asympt.
M	45	T.A.O. ? grade	T.A.O. good collat.	Confirmatory	5 yr. Inter. Cla.
M	30	T.A.O. severe	T.A.O. severe	Confirmatory	3 yr. Inter. Cla.
M	51	T.A.O. severe	T.A.O. severe	Confirmatory	2 yr. Improved
M	46	T.A.O. moderate	T.A.O. severe	Funct. diag.	2 yr. healing
M	42	Abnormal vasoconstriction	T.A.O. poor collat.	Diagnostic	4 yr. worse
M	32	T.A.O. severe	T.A.O. fair collat.	Funct. diag.	3 yr. much impr.
M	43	?Arterial occlusion	T.A.O. fair collat.	Diagnostic	3 yr. Asympt.
M	44	T.A.O. moderate	T.A.O. good collat.	Funct. diag.	5 yr. no change
M	28	T.A.O. severe	T.A.O. fair collat.	Funct. diag.	2 yr. Asympt.
M	56	T.A.O. severe	T.A.O. poor collat.	Confirmatory	2 yr. Inter. Cla.
M	49	T.A.O. severe	T.A.O. severe	Confirmatory	2 yr. Toes Amput.
M	41	T.A.O. mild	T.A.O. good collat.	Confirmatory	3 yr. Asympt.
M	45	T.A.O. fair collat.	T.A.O. poor collat.	Funct. diag.	4 yr. Recur. ulcer
M	28	T.A.O. severe	T.A.O. severe	Confirmatory	2 yr. Recur. ulc's
M	39	T.A.O. severe	T.A.O. some collat.	Confirmatory	2 yr. Recur. ulc's
M	30	T.A.O. severe	T.A.O. poor collat.	Confirmatory	3 yr. Recur. ulc's
M	31	T.A.O. severe	T.A.O. poor collat.	Confirmatory	5 yr. Amput. leg
M	48	T.A.O. severe	T.A.O. severe	Confirmatory	5 yr. worse
M	45	T.A.O. severe	T.A.O. severe	Confirmatory	2 yr. Amput. toes
M	49	T.A.O. severe	T.A.O. poor collat.	Confirmatory	3 yr. Amput. leg
M	59	T.A.O. and arteriosc.	T.A.O. etc. severe	Confirmatory	2 yr. Pregangr's
M	58	T.A.O. and arteriosc. mod.	T.A.O. etc. fair col.	Confirmatory	6 yr. Improved
M	52	T.A.O. and diab. art. severe	T.A.O. etc. poor collat.	Confirmatory	4 yr. Amput. legs

*Abnormal Vasoconstriction*

M	57	Diabetic arteriosc.	Abnormal vasoconstr.	Diagnostic	3 yr. Asympt.
F	24	Diabetic arteriosc.	Abnormal vasoconstr.	Diagnostic	8 yr. Asympt.
F	36	?Arteriosclerotic	Abnormal vasoconstr.	Diagnostic	3 yr. Abn. Vasoeon.
F	34	Arterioscl. severe	Abn. vasoeon., mild arterioscl.	Diagnostic	6 yr. Asympt.
M	49	Abnormal vasoeonst.	Abnormal vasoconstr.	Confirmatory	3 yr. no change

The relation of (a) the diagnosis based on history and physical examination to (b) the diagnosis based on these with the aid of tests.

is normal, unless there is considerable vasomotor tone, the feet become a full pink color, and the veins fill within ten seconds. Arterial occlusion causes a delay in flushing and in venous filling. With severe, uncompensated arterial occlusion the delay may be half a minute or more, and the foot will then become deep red ("rubor") or cyanotic. These tests estimate the status of the arterial circulation only roughly, but are useful because they are simple. Normal variations in vasomotor tone may alter the results. Hypertension may prevent blanching on elevation. Varicose veins rarely allow falsely rapid venous filling in dependent feet.

TABLE IV  
TESTS OF PERIPHERAL ARTERIAL DISABILITY

(A)	Tests which are part of the physical examination. Observation of local tissue nutrition; color of skin and temperature of skin. Palpation of pulses. Rate of blanching on elevation. Rate of flushing and filling of veins on dependency. Blood pressure in different limbs at various levels. Reproducing spasm by immersion of extremity in cold water.
(B)	Tests of Capacity of Blood Flow (Vascular Function Tests) in Skin. Vaso-dilatation Tests. Reflex heat. Heating extremities not tested. <sup>11, 12</sup> Heating the body. <sup>13, 14, 15, 16</sup> Diathermy as source of heat. <sup>22</sup> Artificial fever—Typhoid vaccine. <sup>17, 18</sup> Alcohol ingestion. <sup>19</sup> General anesthesia. <sup>22</sup> Peripheral nerve block with novocaine. <sup>20, 21, 22, 23</sup> Posterior tibial nerve. Ulnar nerves. Other nerves. Spinal anesthesia. <sup>23, 24, 25</sup> Procaine injection into paravertebral sympathetic ganglion chain. <sup>26</sup> Intracutaneous histamine injection test. <sup>29, 30</sup> Intradermal saline wheal test. <sup>31</sup> Reactive hyperemia tests. <sup>37</sup> Arteries of upper extremities. Arteries of lower extremities. Matas' test for collateral circulation. <sup>38</sup>
(C)	Tests of Capacity for Blood Flow (Vascular Function Tests) in Muscle. Walking distance. <sup>40</sup> Ergographic measurements of muscle fatigue. <sup>41, 42</sup>
(D)	Tests of past damage to arteries. Oscillometry. <sup>26, 27</sup> X-ray for calcification of vessels. Arteriography. <sup>43</sup>

#### EXPOSURE TO COLD

Patients who present a history of abnormal vasoconstriction which is not apparent at the time of examination are tested by exposure to cold air or by immersing the affected limb in cold water (15 degrees C. for ten minutes). When the vasoconstriction is confined to the upper extremities, evidence of the presence of a cervical rib and the scalenus anticus syndrome<sup>1</sup> is sought.

## VASODILATATION TESTS

The outcome of physiologic studies on the peripheral circulation is largely influenced by variations in vasomotor tone, that is, the degree of peripheral vasodilatation or vasoconstriction which is present at the time the test is made, for most of the tests estimate the rate of blood flow, and the circulation decreases in proportion to the degree of vasomotor tone. Wide fluctuations in vasomotor tone occur in response to various factors. Vasodilatation occurs in the skin in response to infection, to local heating, to heat applied elsewhere to the body, to a rise in body temperature, and to meals. Blood may flow through exercising muscle as much as ten to twenty times as fast as through resting muscle,<sup>2</sup> and through warm skin as much as a hundred times as fast as through cool skin.<sup>3</sup> Changes in environmental temperature alter vasomotor tone to such an extent that there may be an even faster blood flow in a warm extremity in which there is some occlusion of vessels than in a cool extremity with normal vessels. Consequently, in studying the peripheral circulation it is essential to estimate the degree of vasomotor tone or to remove vasomotor tone at the time the examination is made.

The significant part played by vasomotor tone is illustrated by comparing the physical signs in a limb (a) when there is normal vasoconstriction, and (b) when there is full, normal vasodilatation. When a person feels chilly he usually has a cold, pale foot, and the veins are small and the pulses small or indistinct. When the same person feels warm the feet are warm and pink, and the veins and pulses are prominent.

An example of such a change in the appearance of vascularity is afforded by comparing the two normal feet of a subject after block of the right lumbar sympathetic ganglia with novocain. The left foot is pale, cool (skin temperature 22° C.), and moist; the veins are small, the arteries small, the pulses fine, and the oscillations one space (aneroid sphygmomanometer). Blanching on elevation is complete in 10 seconds, and color returns to the foot and the small veins fill only after forty seconds of dependency. The right foot is bright pink, warm (skin temperature 34° C.), and dry. The veins are large (diameter 3 times those of left), the arteries large (diameter about 2 times those of left), and the pulses are more readily felt than those on the left. Oscillations are two spaces and blanching on elevation is incomplete, and the color returns and the veins fill after three seconds of dependency.

The diagnostic tests which most capably control the factor of variable vasomotor tone are the so-called vasodilatation tests. In these tests, vasomotor tone is either inhibited reflexly or depressed by an anesthetic. After vasodilatation is initiated it continues to its maximum if the conditions of its initiation are maintained. The resulting blood flow equals the undamaged circulation plus the collateral circulation. The collateral,

that is, the nonpulsatile circulation, can then be estimated by comparing this blood flow with the degree of damage estimated from absent pulses and decreased oscillations (see Fig. 4). Vasodilatation tests can measure even a slight decrease in circulation, and measure the circulation in the more distal tissues, where, in patients with peripheral arterial diseases, the ischemia is usually most severe.

As a rule the rate of blood flow in these tests is estimated clinically by measurements of surface temperature. Skin temperature is conveniently measured by means of a thermocouple or skin thermometer.<sup>4</sup> A radiometer is less applicable to the small areas of skin on the tips of digits.<sup>5</sup> Experimentally, plethysmographic and calorimetric methods of measuring peripheral blood flow are used.<sup>6, 7, 8, 9, 10</sup>

A vasodilatation test is performed in the following manner. The patient reclines, lightly clad, in a cool room, preferably in a constant temperature room at 20 degrees C. The feet, or hands, depending upon which are to be studied, are exposed to room air throughout the test. Digital skin temperature is taken at ten-minute intervals, and, when it has decreased to 24-20 degrees C., vasodilatation is reflexly induced by one of several methods. Vasodilatation begins within a few minutes to an hour, depending upon the method used to elicit it. In the normal subject, when vasodilatation is complete the skin temperature of the digits will rise to a level between 31 and 34 degrees C. The methods for inducing vasodilatation include reflex heat,<sup>11, 12, 13, 14, 15, 16</sup> artificial fever,<sup>17, 18</sup> ingestion of alcohol,<sup>19</sup> posterior tibial or ulnar nerve block with procaine,<sup>20, 21, 22, 23</sup> spinal anesthesia,<sup>22, 24, 25</sup> general anesthesia, and injection of the lumbar thoracic ganglion with procaine.<sup>20</sup> Heat cannot, of course, be applied directly to the extremity which is being studied. The skin temperature rises more rapidly in response to anesthetization of the sympathetics than to other procedures, and to a slightly higher level (about 2 degrees C.) because of the lack of sweating and perhaps other factors. With full vasodilatation the temperature of the fingers is normally one or two degrees higher than that of the toes.

The choice of one rather than another means of inducing vasodilatation in the extremities depends upon the subject, and, to some extent, upon the syndrome presented. In any case, the method chosen must produce vasodilatation; if it fails, another method is selected (see Table IV). For the first trial we choose reflex heat because it is innocuous, simple, and is effective in about 90 per cent of the cases. Satisfactory vasodilatation is produced by applying heating pads to the extremities which are not being tested, and covering the body with blankets.\*

Landis and Gibbon<sup>11, 12</sup> immersed the extremities which were not being tested in water at 45 degrees C. Water immersion is cumbersome, but is

\*Pickering has shown that heat applied to a part of the body induces vasodilatation elsewhere by raising the temperature of the blood (ref. *Heart* 16: 115, 1932). Presumably the "vasomotor center" responds to the rise in blood temperature, and lessens vasomotor tone.

even more effective than heating pads in initiating vasodilatation. If reflex heat fails to induce a rise of at least 2 degrees C. in skin temperature, one cannot be sure that vasomotor tone has been abolished, and, although some abnormal vasoconstriction is indicated by this failure, either peripheral nerve block, spinal anesthesia, general anesthesia, or procaine injection of sympathetic ganglia is resorted to. Otherwise, no estimate of the degree of arterial occlusion is gained. When some means other than reflex heat is required (about 10 per cent of the cases), any one of the second choices is nearly always successful in producing maximum vasodilatation.

Vasodilatation tests are, for the most part, easily interpretable (see Table V). Strictly speaking, the interpretation applies solely to blood flow in the skin under the thermocouple, but this is usually representative of surrounding tissues. With a cool room temperature, a rise in skin temperature to 31 degrees C. means that the flow of blood is equal to that of a normal person with full vasodilatation. This level is reached in a limb with no arterial occlusion, or with arterial occlusion which has been completely compensated for by collateral circulation. A rise which falls short of the 31 degrees C. level indicates arterial occlusion—more if the rise is slight, less if the skin temperature approaches 31 degrees C.

Vasodilatation tests are useful (1) in diagnosing or helping to estimate arterial vasoconstriction, (2) in diagnosing early arterial occlusion, (3) in quantitating all but the most severe grades of occlusion, (4) in helping to measure the collateral circulation, and (5) in measuring the capacity for vasodilatation, and hence in deciding about the propriety of vasodilatation therapy, such as sympathectomy. The tests are useful because they remove that important variable, vasomotor tone. They are not indicated in the most severe grades of uncompensated occlusion, for clinical signs and the histamine test afford all of the necessary information in these cases.

#### TESTS OF ABNORMAL VASOCONSTRICTION

Vasoconstriction is a normal, reversible, physiologic process which controls the blood flow to various tissues in accordance with the total economy of the body. Contraction of blood vessels is produced by shortening of the smooth muscle fibers of the media in response to sympathetic nerve impulses or circulating substances.

Before discussing tests for vasoconstriction, it will be necessary to define certain terms. "Normal vasoconstriction" is the degree of contraction of blood vessels which results from physiologic stimuli. It is not sufficiently intense to interfere with tissue nutrition and does not produce signs or symptoms of ischemia. The cool hands of a subject who is exposed to a cold environment illustrate "normal vasoconstriction."



TABLE V  
INTERPRETATION OF VARIOUS VASODILATATION TESTS

PROCEDURE	LEVEL OF SKIN TEMPERATURE RESULTING FROM PROCEDURE	CONCLUSIONS
1. Heat applied to the arms (to test toes); or to legs (to test fingers).	(a) Rapid rise to normal level (31.0° C. or above).	Normal blood flow. (If any occlusion it has been compensated for by the formation of collaterals. Test sufficient.)
	(b) Delayed rise to normal level.	Moderate abnor. vasocon. (Test sufficient.)
	(c) Partial rise, to below normal level.	Effects of organic occlusion, advanced if only slight rise. (Test sufficient.)
	(d) No rise or continued fall.	Abnor. vasocon., but organic occlusion may also be present, so resort to procedure 2, 3, or 4.
2. Posterior tibial (or ulnar) nerve block (to be used only after 1d).	(a) Rise to normal.	*Abnor. vasocon. (If any occlusion it has been compensated for by formation of collaterals. Test sufficient.)
	(b) Partial rise to below normal (in presence of numbness indicating successful injection of nerve).	*Mixture of abnor. vasocon. and occlusion (more rise indicates less occlusion, test sufficient).
	(c) No rise, or continued fall (in presence of numbness, etc.).	*Abnor. vasocon., but organic occlusion probably also is present, so resort to procedure 3, or 4.
3. High spinal anesthesia (applicable only for leg symptoms).	Same as 2.	*Same as 2.
4. Novocain injection of sympathetic chain (lumbar or dorsal).	Same as 2.	*Same as 2.

\*Routinely only the group 1d is chosen for procedure 2, 3, or 4. If patients previously untested are chosen for procedure 2, 3, or 4, conclusions should be as under 1.

"Abnormal vasoconstriction" is an excessive contraction of blood vessels in response to physiologic stimuli, or contraction as a result of abnormal stimuli. The vasoconstriction is sufficiently intense to interfere with the normal metabolic demands of the tissues and produces signs and symptoms of ischemia. The results of abnormal vasoconstriction are, usually, coldness, cyanosis, and pain, and, ultimately, superficial necrosis. "Abnormal vasoconstriction" is frequently seen in association with organic vascular occlusion, as in thromboangiitis obliterans.

"Vasospasm" is a term which has been loosely used to indicate abnormal vasoconstriction. It seems to us that it should be used specifically to denote an actual spasm of blood vessels, with complete circulatory arrest. The classical manifestations of vasospasm occur in the blanched fingers of patients with Raynaud's disease. It may also follow arterial trauma, as in acute embolism of peripheral arteries, and is occasionally seen in patients with acute iliofemoral thrombophlebitis. Prolonged spasm, although rare, will cause gangrene.

"Capacity for vasodilatation" is the measured increase in circulation which occurs when vasoconstrictor tone is removed, as it is in one of the vasodilatation tests. It does not necessarily mean that "vasospasm" or "abnormal vasoconstriction" is present, but simply indicates that the blood vessels have an increased capacity when the vasoconstrictor tone is removed. Some capacity for vasodilatation is a prerequisite for a diagnosis of normal or abnormal vasoconstriction or vasospasm.

#### TESTS OF VASOCONSTRICTION

With these definitions in mind, vasoconstriction is revealed clinically by intermittent coldness, blanching, or cyanosis, and is frequently associated with excessive sweating, or pain, in a limb which has its pulses and at least some capacity for vasodilatation. No tests have been devised to differentiate between normal and abnormal vasoconstriction and vasospasm. If the patients are free from symptoms at the time of examination, exposure to cool air or the immersion of an extremity in cold water may help establish the diagnosis of abnormal vasoconstriction. When vasodilatation produced by reflex heat fails to relieve vasoconstriction, and relief is obtained by more vigorous procedures such as anesthetization of sympathetic nerves, the patient can be said to have abnormal vasoconstriction, but there are other patients with undoubtedly abnormal vasoconstriction who obtain prompt relief from reflex heat.

Vasoconstriction produces ischemic symptoms which are indiscernible from those of organic arterial occlusion. The vasodilatation tests play an important part in the study of various grades of vasoconstriction, in that they measure the capacity for vasodilatation, thereby excluding, or measuring the degree of, organic occlusion. It is most difficult to differentiate vasoconstriction from occlusive vascular disease when the latter is accompanied by abnormal vasoconstriction. In such cases, careful attention to the history, examination, and vasodilatation tests gives a remarkably accurate picture of the abnormal vascular system.

#### OSCILLOMETRY

Clinical oscillometry affords a measure of the total pulsation transmitted by the heart's beat to the vessels encompassed by the oscillometer cuff.<sup>26, 27</sup> In normal subjects, arteries large enough to carry a palpable pulse contribute most of the pulsation, and the smaller arteries and arterioles make up the rest. Aside from alterations in the strength or rhythm of the heartbeat, the oscillometric readings in a limb become abnormal because of several common disturbances in the peripheral arterial circulation. The oscillations are lessened (1) by obstruction to the pulse wave, such as that caused by arterial occlusion and aneurysm, even in the presence of an adequate collateral circulation, and by arterial or arteriolar spasm, (2) by lessened flexibility of arteries and arterioles, such as occurs in arteriosclerosis, (3) by a diminution in the size of the arterial, arteriolar, and probably venous bed, (4) by a profound decrease

in blood pressure, and (5) by an inflexible, tight skin such as that of scleroderma. The oscillations are increased (1) by vasodilatation, whether it be physiologic or pathologic, and (2) by escape of arterial blood directly into veins, as with single or multiple arteriovenous fistulas.

Great fluctuations in blood flow, such as are induced by cold and heat in the skin, and by rest and exercise in muscle, change the oscillometric readings. In a normal subject with peripheral vasoconstriction oscillometric readings from a finger are increased about sixfold, from a toe about threefold,<sup>3</sup> and from the ankle about twofold when full peripheral vasodilatation is induced by heat. Oscillometric readings from the resting calf are about doubled immediately after exercise, in spite of a concomitant slight decrease in the blood flow through the skin of the calf. Therefore, if minimal oscillations are rated as 0, and maximal normal oscillations as 1, the range of normal at ankle level is between  $\frac{1}{2}$  and 1 when the subjects are under controlled conditions with respect to exercise and warmth. The amplitude of the oscillations is more nearly standardized when measurements are made only after vasomotor tone is released, or when, in a single subject, readings are compared at identical levels of the two legs. Slight discrepancies in adjustment of the cuff still contribute some error. Muscle spasm, anomalous arteries, cardiac weakness, severe scleroderma, and the size of the subject rarely confuse the interpretation.

The clinical use of oscillometry is most helpful (1) in ascertaining the exact level of arterial occlusion, (2) in helping to establish the presence or absence of pulses which are not palpable because of overlaid muscle, fat, or edematous tissue, (3) in measuring past vascular damage which may or may not have been compensated for by a nonpulsatile collateral circulation, (4) in detecting the site of arteriovenous fistulas, and (5), when combined with a vasodilatation test in estimating the extent of the collateral circulation (when collateral circulation equals blood flow minus undamaged circulation).

Several types of oscillometers are available for clinical use; in all of them the pulsations are transferred from a cuff to a tambour with a recording needle. A recording instrument has the advantage of producing a permanent record. The ordinary aneroid sphygmomanometer is a nonrecording form of oscillometer which is satisfactory for most purposes. With this instrument the normal reading at the ankle is between one and two scale markings, when each marking indicates 2 mm. Hg. Similar instruments which are marketed as oscillometers have larger and more easily read scales.

#### CUTANEOUS HISTAMINE REACTIONS

Unless there is marked cutaneous vasoconstriction, histamine, when introduced into the skin of a normal person, produces a localized wheal within three minutes after injection. If the blood flow to the part has been completely arrested no wheal appears.<sup>28</sup> If the blood flow is greatly

decreased, either the wheal will not appear or its appearance will be delayed.<sup>29, 30</sup> Starr has utilized this phenomenon as a measure of blood flow. Any delay in wheal formation of more than five minutes indicates severe ischemia. When no wheal appears the life of the tissues is endangered, and gangrene is usually imminent unless blood flow can be made to increase. Moderate grades of occlusive disease fail to alter the time of appearance of the wheal.

This test, like the vasodilatation test, is a test of capacity for entaneous blood flow only, but this is hardly a limitation because failure of the entaneous circulation is the cause of most of the more serious consequences of peripheral vascular disease. The histamine test is more sensitive than the vasodilatation test only in the lowest range of blood flow estimated by the latter.

The test is performed by placing a small drop of 1/1,000 histamine acid phosphate on dried, cleaned, nonedematous skin (preferably not over bone), by needling the skin several times through the drop, and by feeling for a wheal.\* Any palpable irregularity is considered a satisfactory wheal. A necessary precaution is that vasoconstriction be relieved before this test for arterial occlusion is performed; a cold, white, or blue skin should be prepared by gentle warming. There are exceptions in Raynaud's disease and in acrocyanosis, as described below.

The histamine test is indicated mainly when occlusive arterial disease is known to be present. We have never seen a wheal fail to appear within five minutes, when the test was properly performed, in patients who have a fairly good or good entaneous circulation, as indicated by the vasodilatation test. The reaction is unaffected by moderate degrees of arterial occlusion; the test is sensitive to slight changes in severe arterial occlusion. It is most useful in making a prognosis of the viability of ischemic tissues. Skin which fails to develop a wheal after histamine injection, when the precaution against vasoconstriction has been taken, is too ischemic to enable incisions to heal, whereas delayed wheal formation indicates that healing is improbable. Wheal formation within 3 to 5 minutes indicates that there is sufficient blood flow for the healing of incisions, but infection, because of its great demands on blood flow, can upset conclusions based on the histamine test. The test should not be performed on, or adjacent to, necrotic tissue, but is sometimes most useful a few centimeters above a line of demarcation. The test is sometimes helpful in determining the lowest level at which an amputation wound can be expected to heal, but in this connection Starr has emphasized the need for taking all data available into account in deciding the question whether amputation should be done, and at what level.

The test is useful in differentiating between Raynaud's disease and acrocyanosis. In Raynaud's disease the spasm is predominantly in the small and large arteries, and, in acrocyanosis, in the arterioles. When

\*Histamine for this purpose can be kept for months when chlorethane is added to make a 1 per cent solution.

histamine is needled into the skin it does not reach the arteries, and so it fails to produce a wheal in the white, cold fingers of a patient with Raynaud's disease. In the ischemic, mottled, red or blue, cold skin of acrocyanosis, histamine produces a brilliant flare and conspicuous wheal. In the presence of peripheral neuritis a flare may not appear, but the wheal is not affected.

Starr has studied the prognostic value of the histamine test on the feet of patients with diabetes. Of eight-nine patients with diabetes who were followed for five years, none with a normal reaction developed any serious vascular trouble. Of the thirty-two patients who gave markedly impaired reactions, eighteen died, and only five survived the five-year period without serious lesions of the feet.<sup>29</sup>

#### THE INTRACUTANEOUS SALT SOLUTION WHEAL TEST

Stern and Cohen<sup>31</sup> adapted to studies of peripheral arterial circulation the test that McClure and Aldrich<sup>32, 33</sup> used to investigate edema. They found that a wheal which resulted from the intracutaneous injection of physiologic saline disappeared more quickly in markedly ischemic skin than in skin with a normal blood supply. The test is less well standardized and less quickly performed than the histamine test, which appears to have supplanted it.

#### REACTIVE HYPEREMIA TESTS

Reactive hyperemia, i.e., an increase in the flow of blood above what is normal for the limb, results after relief of temporary circulatory arrest.<sup>34</sup> To perform this test the blood is drained out of the foot by elevation, and the little color remaining in the foot is pressed out manually. A blood pressure cuff is then placed around the thigh with the leg in the elevated position, the cuff is inflated to a pressure greater than systolic pressure, and the foot is then lowered to the horizontal position. The blanched appearance of the foot is preserved. Sudden release of the pressure in the cuff results in a rapid flush which is occasioned by inflowing blood, except when there is arterial spasm or occlusion. Lewis and Grant<sup>35</sup> and Freeman<sup>36</sup> have studied the mechanism of the vasodilatation produced by the ischemia prior to release of the cuff. Pickering<sup>37</sup> standardized the conditions which are necessary when the phenomenon is used as a test of arterial occlusion. The foot is warmed in water at 35° C. for ten minutes, and occlusion is then maintained for five minutes. In a limb with normal vessels the flush is complete within three seconds after release of the cuff pressure. The flush is delayed in extremities with occluded arteries in proportion to the extent of the occlusion, and occurs evenly or unevenly, depending upon the distribution of the occlusion. The duration of maintenance of cuff pressure should be lessened when severe arterial occlusion is suspected.

When reactive hyperemia is used to test for arterial occlusion in the upper extremity, the hand is raised, the fist closed, the wrist grasped

tightly by the observer, the hand lowered, opened, and, after three minutes, the wrist released. Heating the hand is less necessary than heating the foot because vasomotor tone is less readily maintained in the hand. The resulting flush is interpreted in the same way as that in the foot. A useful modification serves to demonstrate patency or occlusion of the ulnar artery when the ulnar pulse cannot be palpated. The modification follows the above directions, with the addition that the radial pulse is held compressed from the time the pressure is being released. Care should be taken that compression of the radial be prevented from extending to the ulnar artery. In like manner, occlusion of a single one of the paired digital arteries can be demonstrated. These modifications of the test are occasionally of diagnostic value early in the course of thromboangiitis obliterans.

One of the earliest forms of the reactive hyperemia test is the most complete, and, in its special application, the most useful. Matas<sup>35</sup> designed the test to estimate the extent of the collateral circulation in a limb with an arteriovenous fistula prior to operation. The whole circulation is arrested by an Esmarch bandage, and the main artery just above the fistula is compressed digitally or instrumentally to a degree sufficient to occlude it. The bandage is removed while arterial compression is maintained. Reactive hyperemia results through the collateral circulation only. The test demonstrates the extent of the collateral circulation, and, therefore, shows whether or not it is safe to undertake surgical procedures such as ligation and excision. Halstead<sup>36</sup> suggested a somewhat similar procedure, in which a metal band is adjusted so that it will partly occlude an artery above an arteriovenous fistula. This procedure is both a test and a therapeutic method. The tightness of the band is repeatedly adjusted to maintain a barely adequate blood flow, thus diminishing the symptoms from the fistula and encouraging growth of collateral circulation without causing undue ischemia. An opportunity is thus afforded for final arterial closure with lessened danger to the limb.<sup>38, 39</sup>

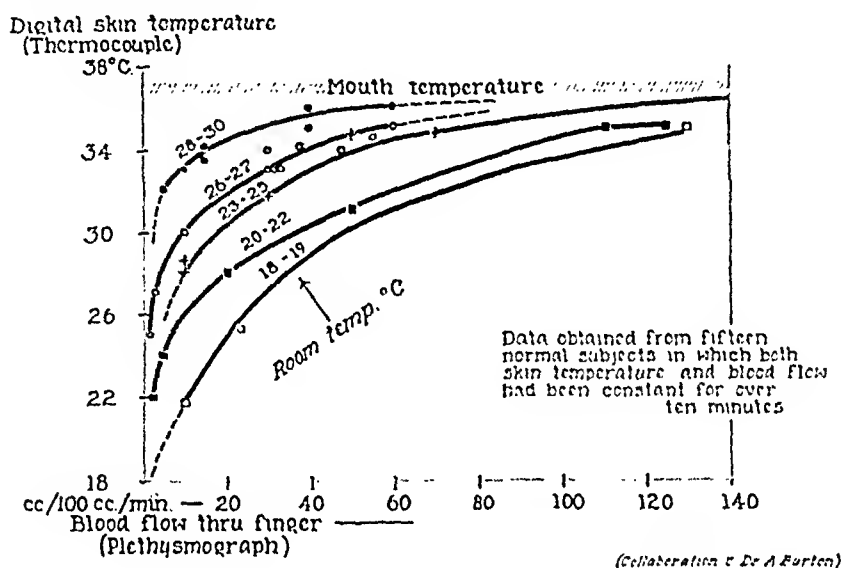
#### METHODS OF ESTIMATING BLOOD FLOW THROUGH MUSCLE

##### (TESTS OF INTERMITTENT CLAUDICATION)

Intermittent claudication results from interference with normal arterial blood flow through muscle. An adequate estimate of muscle blood flow can usually be obtained from the patient's statement concerning the walking distance necessary to precipitate pain, or more accurately by having the patient walk at some standard rate, such as 120 steps per minute.<sup>40</sup> A satisfactory estimate can be made by having the patient alternately press and raise the foot against a pedal.<sup>41</sup> The most objective method of measuring intermittent claudication in the muscles of the calf is that of Hitzrot, Naide, and Landis.<sup>42</sup> In the operation of this test the patient reclines, with the foot resting against a board which is supported by a spring. A uniform electrical stimulus



Fig. 2 shows the clinical significance of the skin temperature of digits with maximal vasodilatation and a room temperature of  $21^{\circ}\text{C}$ . ( $70^{\circ}\text{F}$ .), and illustrates the capacity for vasodilatation within the digits. The normal skin temperature, with maximal vasodilatation, of a toe is about  $31^{\circ}\text{C}$ . At  $29^{\circ}$  the skin temperature is subnormal but "good"; at



(Collaboration of Dr A. Burton)

Fig. 1.—Relationship of digital skin temperature to blood flow through adjacent finger.

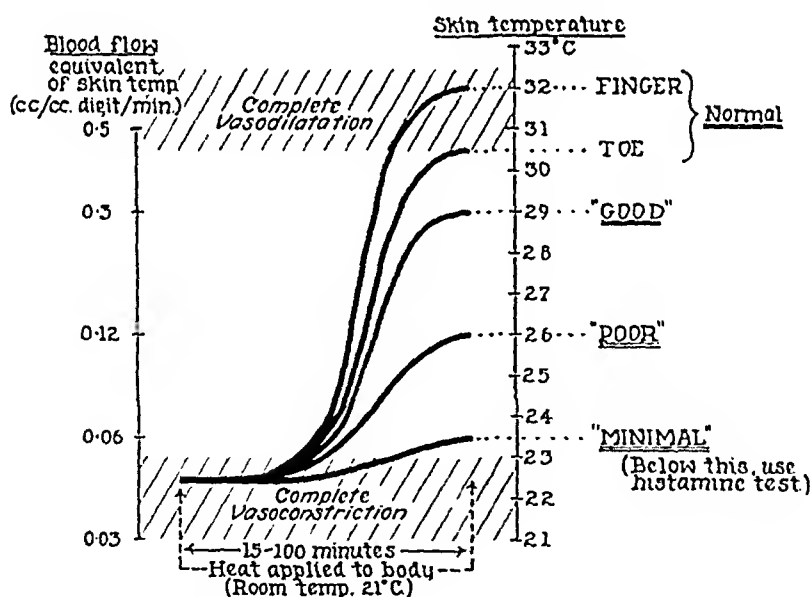


Fig. 2.—Clinical significance of digital skin temperature.

$23^{\circ}$  it is "minimal," and gangrene is imminent. With this low capacity for vasodilatation, and here only, the histamine wheal test offers a finer differentiation of functional capacity.

By and large, oscillations and pulses are closely similar measurements of past damage. Fig. 3 illustrates this relationship. Ankle pulses are plotted against oscillations at the ankle. Absent pulses and minimal



oscillations and normal pulses and maximal oscillations correspond well. Neither oscillometry nor pulses, however, necessarily indicate functional capacity. In Fig. 4 ankle pulses are plotted against digital skin temperature when there was maximal vasodilatation in the toes.\* Although with severe, uncompensated occlusion there are usually no pulses and

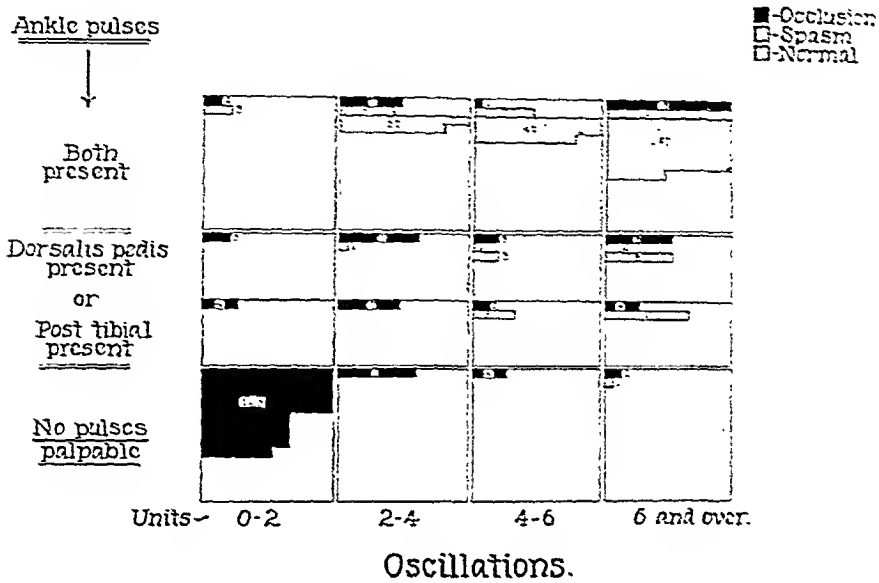


Fig. 3.—Relationship of ankle pulses to oscillometric readings. Each large square represents 200 legs.

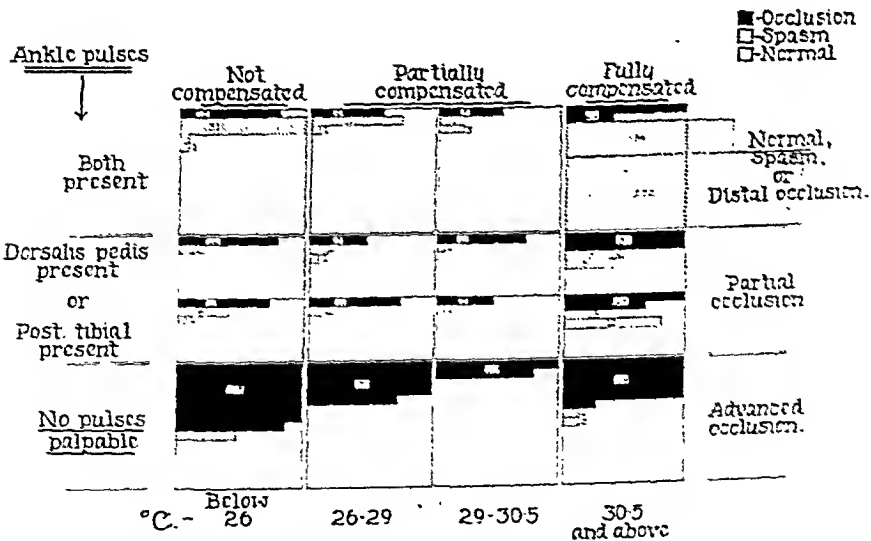


Fig. 4.—Relationship of ankle pulses to capacity for vasodilatation. Each large square represents 200 legs.

a low skin temperature, and normal limbs usually have both ankle pulses and a high skin temperature, there were 176 limbs in which there were no pulses and yet considerable blood flow. These observations are interpreted as evidence of fair to excellent function of a nonpulsatile

\*A graph of oscillations versus skin temperature with maximal vasodilatation has been omitted because it is essentially the same as that of pulses versus skin temperature.

collateral circulation. Other points which fall out of line with good pulses but lessened function are interpreted as abnormal vasoconstriction\* or distal occlusion. The data on nonpulsatile collateral flow are again presented in Fig. 5. This figure shows the results obtained from the vasodilatation test on all limbs in which no ankle pulses were felt. The

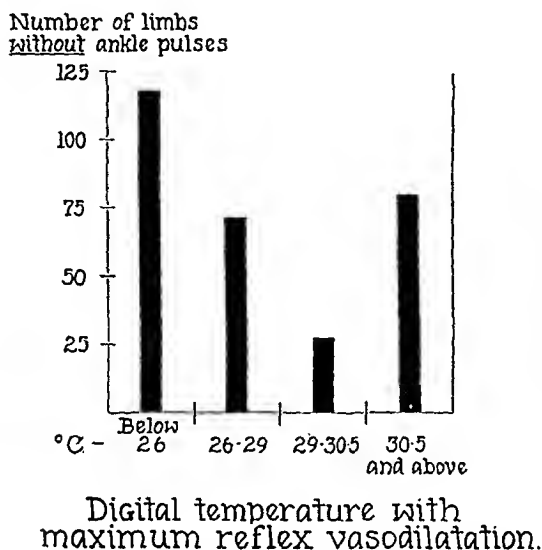


Fig. 5.—Vasodilatation test in patients with arterial occlusion.

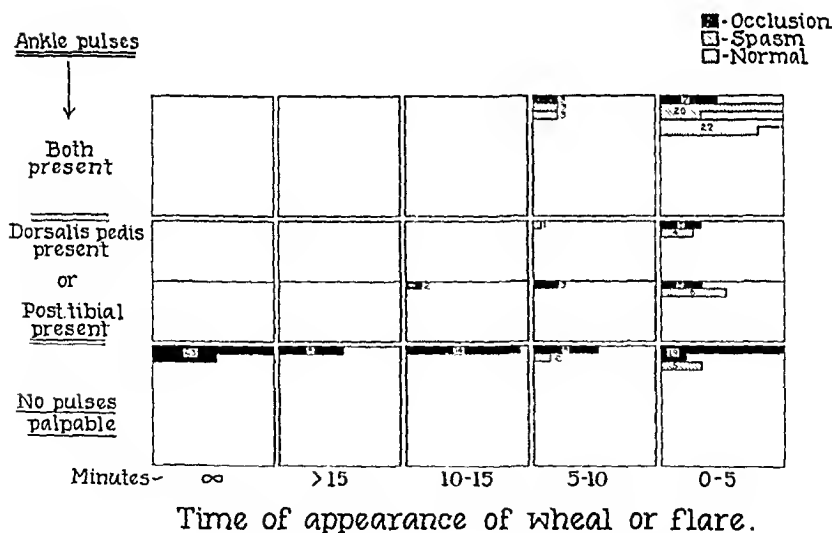


Fig. 6.—Relationship of ankle pulses to histamine test. Each large square represents 200 legs.

largest group of these limbs had poor function, but there were three other large groups in which the function was fair or even excellent, showing the great frequency with which a collateral circulation follows severe damage.

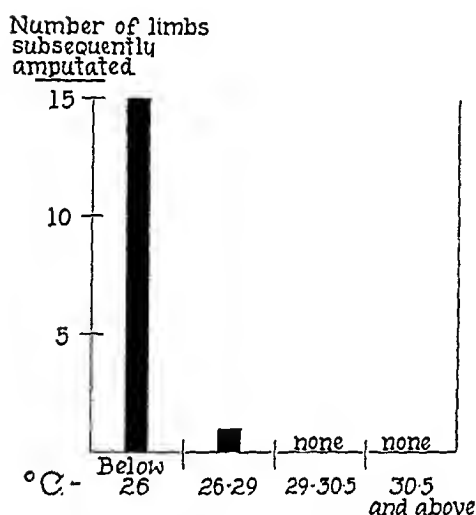
That the pulse wave does not necessarily indicate the functional

\*For simplicity in Figs. 3, 4, and 6, "abnormal vasoconstriction" has been termed "spasm."

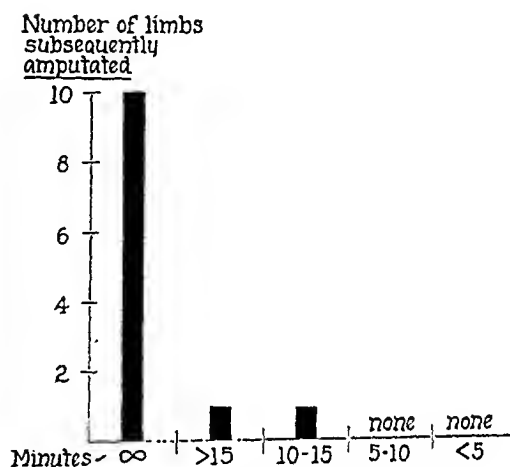
capacity of the vessels is shown also in the graph of histamine test versus ankle pulse (Fig. 6).

The prognostic significance of the vasodilatation test and of the histamine test is shown in Figs. 7 and 8. Amputation is seldom required if the vasodilatation test or the histamine test shows good function.

A structural and functional classification of conditions of the peripheral arteries is presented in Table II. Prognosis and therapy follow principles already indicated, but are of course influenced by knowledge gained from the history, physical examination, conventional diagnosis, and a knowledge of the metabolic needs of the peripheral tissues. Especially if there is a lesion, the metabolic needs may determine prognosis quite as much as does the capacity for blood flow.



Digital temperature with maximum reflex vasodilatation.



Time of appearance of wheal or flare.

Fig. 7.—Clinical significance of vasodilatation test.

Fig. 8.—Clinical significance of histamine test.

#### SUMMARY

In peripheral arterial disease there are two major processes at work: (1) obstruction of arteries and (2) formation of collateral circulation. Either damage or repair may become dominant. Collateral circulation means functional repair. Vasodilatation tests, the histamine test, and reactive hyperemia tests are tests of function, and when past vascular damage is estimated by oscillometry or palpation of pulses these tests help to estimate the extent of the collateral circulation. Superimposed abnormal vasoconstriction may confuse the picture. Only by evaluating the circulation from the standpoint of past damage, its extent and location, repair, functional capacity, and superimposed vasomotor tone can the clinical status of each individual patient be entirely appreciated. Various tests of peripheral arterial conditions are important adjuncts to information gained from a complete history and physical examination.

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#### DISCUSSION

DR. NELSON W. BARKER (Rochester, Minn.).—I think that this presentation is an excellent statement of the problem of study in cases of peripheral vascular disease. Two comparatively simple tests were not discussed: (1) The claudication test, which can be done in several different ways, either with apparatus or by having the patient take a fixed number of steps per minute under standard environmental conditions in order to ascertain the time necessary for claudication to develop. This is a test of the functional capacity of the circulation of the muscles, whereas most of the other tests measure the functional capacity of the circulation of the skin. (2) The elevation-dependency test, the value of which I would like to emphasize. This requires no apparatus, but should be done under controlled environmental temperatures, and, when comparative tests are made, they should be done at the same time of the day and at the same time after ingestion of food. The patient's feet should be elevated for a fixed period until maximal blanching has occurred; then the feet are rapidly placed in the dependent position, and the time required for

the color to return is recorded. This simple test gives considerable information as to the functional capacity of the circulation of the skin of the feet.

I would like to emphasize another fact which has some bearing on prognosis. Arterial insufficiency of considerable degree which has come on rapidly may be a much greater hazard as far as the development of gangrene is concerned than the same degree of arterial insufficiency which has come on gradually or has been present for a considerable period of time. The tissues may develop a capacity to exist under conditions of considerable ischemia if it does not develop too rapidly.

DR. D. W. KRAMER (Philadelphia).—I was pleased to hear Dr. Montgomery's paper. I think circulatory function tests have now reached the point where they are considered as necessary procedures in diagnosing peripheral vascular disorders.

It is now generally recognized that a history and an examination of the peripheral pulses are not sufficient because the patient may have a good dorsalis pedis pulse and still have gangrene. On the other hand, the dorsalis pedis pulse may be absent even when the patient has an efficient circulation.

There are about thirty tests which may be employed. Some of them are more practical than others. Some are prohibitive because of their expense and can only be employed in hospitals and clinics.

I was glad to hear Dr. Montgomery discuss the oscillogram. This method of studying the circulation has been unduly criticized. Although it has its drawbacks, it does give definite information, particularly pertaining to mass pulsation of the larger vessels.

The histamine test is a simple procedure that is inexpensive and can be performed in the office. It gives us definite information as to the capillary response and, indirectly, the condition of the underlying vessels.

Calorimetric and thermometric studies are helpful in deciding whether we are dealing with organic occlusive conditions or vasospasm. However, all of these tests still require checking up and further investigation.

Even our views concerning skin surface temperature studies, which we accept as our most reliable method, may some day require modification. At the present time I have two patients who apparently have the classical clinical manifestations of thromboangiitis obliterans, but their skin surface temperature can be made to rise to maximum limits. This would indicate that we were dealing entirely with vasospasm, but I doubt whether this was true in these particular cases.

I hope that others will continue to investigate the various circulatory function tests and help establish their value in interpreting the various pathologic disorders of the peripheral circulatory system.

DR. HUGH MONTGOMERY (Philadelphia).—There is, of course, a long list of tests. We started out to discuss approximately twenty-five of them, but saw that this was impossible.\*

Certainly the claudication test has considerable value, although I think not as much as some of the others, because walking alone will give very good information concerning the function of the calf or foot muscles, except in unusual circumstances.

I do not altogether agree with Dr. Barker that the elevation and dependency test is fairly accurate. We look on it more, I think it is fair to say, as a part of the physical examination. Very useful information can be gained from it, as it certainly can be from the physical examination in general, and we are not trying in any way to leave the impression that these tests take the place of a thorough physical examination.

I was wondering whether Dr. Kramer's patient was not one who did have thromboangiitis obliterans, but nevertheless had perfectly normal function—in other words, a patient who had obtained his collateral circulation.

\*This paper was shortened for verbal presentation and now is presented in full.

# Department of Clinical Reports

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## PAROXYSMAL TACHYCARDIA IN INFANCY

### REPORT OF CASE

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**P**AROXYSMAL tachycardia in infancy is a relatively rare condition. The youngest patient with this condition, reported by Werley,<sup>1</sup> was an infant 4 days old. Doxiades<sup>2</sup> has reported a case in a 7-day-old infant. Farr and Wegman<sup>3</sup> reported a case in a 24-day-old infant, and Colgate and McCulloch<sup>4</sup> in a 3-week-old infant. Von Bernuth and von den Steenen<sup>5</sup> observed the condition in a 3-week-old child; Schuster and Paterson<sup>6</sup> reported two cases, one in an infant 9 weeks old and another in an infant 2 months old. O'Flynn<sup>7</sup> reported a case in an infant 8 months old, and Koplik<sup>8</sup> a case in an infant 22 months old. Lyon<sup>9</sup> also reported a case in a child 31 days of age. Reports of cases occurring in children over the age of 2 years are more numerous. Taran and Jennings<sup>10</sup> have cited fifty-two cases occurring in infants and young children. Clark<sup>11</sup> has also cited many cases in older children.

The etiology of paroxysmal tachycardia is obscure. In some cases post-mortem examinations have revealed definite cardiovascular changes, while in other cases there have been no demonstrable changes. In several cases the tachycardia was apparently the result of or a sequela of an organic disease such as encephalitis, chorea, or muscular dystrophy. Again the attacks ran concurrent with or followed such conditions as measles, whooping cough, or other infectious diseases. In some cases congenital heart conditions apparently acted as causative factors. However, it has been frequently noted that many of these attacks followed a mild upper respiratory infection.

The main purpose of this paper is to report a case of paroxysmal tachycardia in an infant 2 months old.

This patient, a white male, was the firstborn of a 34-year-old mother. He was delivered by medium forceps following a long labor. The child's condition was good at the time of birth. Two weeks following birth the child was examined by a pediatrician, who found no evidence of birth injuries nor of any congenital anomalies.

The patient was seen on March 8, 1938, at 9:00 P.M., and was diagnosed as having a very mild sore throat. The temperature was 99.6° F. by rectum. The heart rate was too rapid to count. There was no evidence of cardiac failure at this time. The following morning the child was seen again, and at this time he still had a very rapid heart rate. There was definite enlargement of the liver, and the spleen

could be palpated. There was very little cyanosis. The patient was hospitalized on March 9, 1938. On admission, oxygen was started, and morphine sulfate,  $\frac{1}{150}$  gr., was given every four hours. Pressure was applied to the vagus nerve and to the eyeball, without any slowing of the heart rate. Vomiting was induced with ipecac, but this too failed to stop the tachycardia.

An electrocardiogram showed a regular rate of 291 per minute. A teleroentgenogram of the chest did not show any enlargement of the heart. The urine and results of other laboratory tests were well within the limits of normal. Since the child refused nourishment, a hypotonic solution of glucose was given intravenously.

On the following day (March 10) there was very little change in the patient's condition. He refused his feedings but took water in small quantities. At 2 o'clock in the afternoon the patient was given 10 minims of digifolin subcutaneously. Two hours later the dose was repeated. At 5:30 p.m., the heart rate dropped to 140 per minute, and the patient's general condition improved. He began to take his feedings, and he was dismissed from the hospital on the following day. Apparently he had recovered completely.

On March 25, seventeen days following the initial attack, the child had another attack. He was given 10 minims of digifolin shortly after the onset, and this dosage was repeated every eight hours. The heart resumed its normal rate on March 27, after three doses of digifolin. The third attack occurred thirteen days after the second; again digifolin was given, and the heart returned to normal in twelve hours' time. On April 10, three days later, there was another attack which lasted sixteen hours and required two doses of digifolin. Ten days later another attack occurred which lasted twenty-four hours. Four doses of digifolin were given before the rate returned to normal. The sixth attack occurred forty-seven days later and lasted twenty-four hours. At this time two doses of digifolin were given. The seventh attack began July 29, or thirty-seven days later, at 3:30 p.m. We did not use digifolin until the next day at 12:45 p.m. The heart rate dropped to 175 per minute in an hour and slowed to 140 in another hour.

Since this last attack, the child has been free of the irregularity. At this time, almost two years later, he is apparently healthy and even more vigorous than the average child of 2 years.

The treatment of paroxysmal tachycardia has been extremely varied. Some clinicians have used oxygen, digitalis, morphine, quinine bisulfate, and quinidine. In certain cases quinidine therapy apparently exaggerated the condition. Several cases have resulted in death, regardless of treatment. Other cases have ended spontaneously. Shookhoff, et al.<sup>12</sup> used digitalis, phlebotomy, quinidine sulfate, and quinine urea hydrochloride in their case, without result. Later, however, when decompensation occurred, the child responded to digitalis. Farr<sup>3</sup> and Van Cleve<sup>13</sup> reported cases in which digitalis was of benefit. Meeholyl has been used by Wright,<sup>14</sup> with good results. This treatment was suggested in our case, but we were under the impression that this drug was rather dangerous in infancy. I believe that digitalis is probably the best drug to use in this condition. Certainly it is the best drug for patients who show any signs of cardiac decompensation.

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## VEGETATIVE ENDOCARDITIS IN AN AURICULAR SEPTAL DEFECT

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**"V**EGETATIONS, while common on the margins of the interventricular septal defect, patent ductus or malformed valvular orifice, almost never occur on the interauricular septum." This constitutes a recent statement of Maude E. Abbott<sup>1</sup> in a personal communication. In her series of 850 cases of congenital cardiac anomalies, only one case, and that a case of subacute bacterial endocarditis upon a lower auricular septal defect, was found. This rarity has also been stressed by White.<sup>2</sup> No report of a substantiated case of an acute process with fresh vegetations has been found by the author. For these reasons, the following report of a very unusual pathologic picture is presented.

During the progress of experimental investigations upon resection of the lower third of the esophagus, an apparently healthy female dog was used. The estimated age of the dog was 4½ years, and the weight was 20.4 kg. For two weeks prior to operation the animal had been observed in the isolation room, and although no cardiac studies had been carried out, the animal was considered to be in good health. Daily records are made of the pulse rate, rectal temperature, and respiratory rate of dogs subjected to this experimental procedure, in order that a true preoperative base line can be found for postoperative comparison. The results in this case fell within what was considered to be the normal for such dogs: temperature, 100.8 to 102.6° F.; pulse, 90 to 120; respirations, 18 to 24.

Under combined morphine and nembutal anesthesia, a resection of the cardiac end of the stomach and the lower third of the esophagus was performed. During this transthoracic procedure, the cardiac action could be directly observed and was not unusual. No direct pericardial or cardiac injury was occasioned by the operation. No untoward effects from either the anesthesia or the operation were noted, and within twenty-four hours the animal was again in apparently good health. The postoperative course remained smooth and uncomplicated until the fourth postoperative day when the rectal temperature rose to 103.2° F. from a previous level of 101.6 to 102.4° F.; respirations rose from 24 to 36, and pulse from 120 to 130. Roentgenograms and physical examination of the chest corroborated the impression of atelectasis in the lower lobe of the left lung. Diagnostic aspiration of the pleural cavity was negative. Following hyperventilation, the clinical findings disappeared within a few hours, and the course remained uneventful until the eighth postoperative day, when a slight wound infection was found. This persisted in mild degree until the dog's death, fourteen days following operation. A precipitous drop in temperature to 99.6° F., without change in pulse or respiration, occurred on the tenth postoperative day. The pulse gradually increased from then until the thirteenth postoperative day, as did also the rectal temperature and respiratory rate. The clinical impression of auricular fibrillation and marked general toxicity was noted on the thirteenth postoperative day, and the animal was found moribund the morning of the fourteenth postoperative day.

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At autopsy, a mild infection of the lower end of the chest wound was found, but the operative area showed primary healing of the anastomosis, without perforation or stricture. Both pleural cavities were free of fluid and exudate, but the presence of multiple petechiae scattered diffusely about the periphery of the lungs was noted. There was no gross pneumonia but a marked, diffuse pulmonary edema. The right ventricle of the heart was considerably dilated, and on opening of the pericardium, it was evident that intravascular clotting had occurred recently in the descending branch of the left coronary artery (Fig. 1). An antemortem thrombus was found on opening this vessel. Infarction was demonstrated by the discoloration of the surrounding 2 cm. of myocardium and by the small



Fig. 1.—Area of denuded epicardium and infarction about the left descending coronary artery. Some small petechiae can be seen on the specimen of the lung.

area of denuded epicardium overlying this area. Thirty cubic centimeters of blood-tinged fluid was found in the pericardial cavity. On opening the heart, no mural thrombi were found, but an interauricular septal defect, as shown in Fig. 2, was discovered. This consisted of an opening 6 mm. in diameter, and at its edge on the left auricular side three fresh, globular vegetations were present. Scattered smaller vegetations were found along its intraseptal course. The remaining cardiac chambers, as well as the great vessels, showed no abnormalities either as to position, diameter, or configuration. The valvular structures throughout were delicate and apparently competent. Gross evidence of embolic phenomena were easily discernible

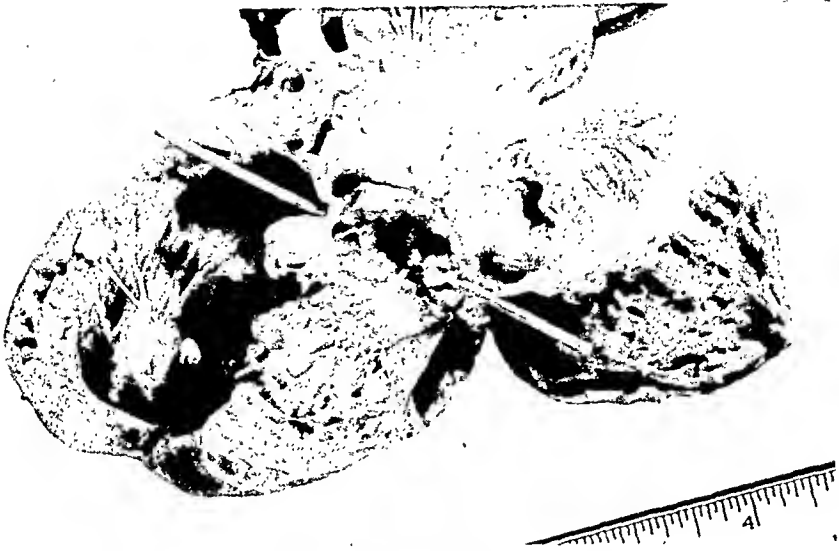
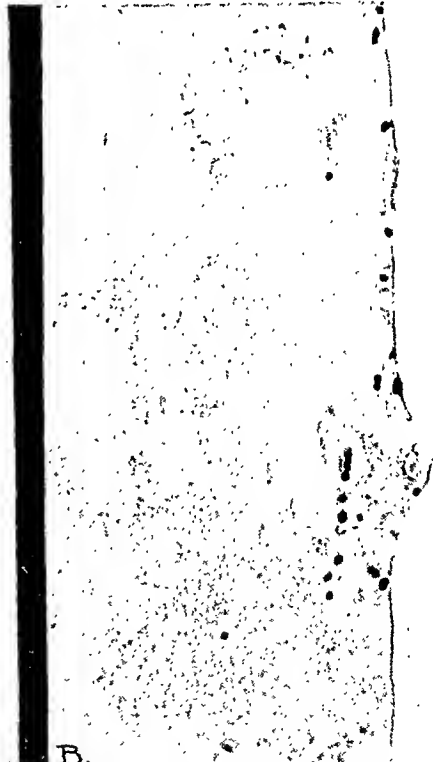


Fig. 2.—Interauricular communication through which a probe is passed, and the fresh vegetations about one orifice.



A.



B.

Fig. 3.—A, Photomicrograph of section taken through area of the septal defect, showing interauricular and interventricular septa. Portions of valves and large vegetations are seen. This section is oblique to the channel and shows only the opening on the left auricular side. The lowest portion of the interauricular septum is distorted by technique in cutting. (X15.)

B, Photomicrograph of area inclosed by circle in A, demonstrating organisms, fibrin, and platelets. (X1200.)

on the cut surfaces of all lobes of the lungs, in the right cerebral cortex, the parenchyma of both kidneys, the cortex of the right suprarenal gland, and the spleen.

It is unfortunate that no cultures of the fresh tissues were made, but microscopic study of the involved organs revealed multiple septic infarcts, and on bacteriologic study, large groups of a gram-positive diplococcus were found. Sections for microscopic study made through the infarcted area about the left coronary artery showed evidences of fresh infarction with polymorphonuclear leucocytic infiltration about groups of bacteria similar to those previously described. Sections through the interauricular septum revealed a peripheral area of fresh abscess formation, as well as considerable deposits of fibrin, groups of platelets, and bacteria in the vegetations themselves (Fig. 3, *A* and *B*).

#### CONCLUSIONS

A case of a dog with postoperative acute bacterial endocarditis superimposed upon a congenital interauricular septal defect is presented. Embolic manifestations of a paradoxical nature occurred. The extreme rarity of this complication and the possible interest to other investigators prompted this report.

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# Department of Reviews and Abstracts

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## Selected Abstracts

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Chen, K. K., and Elderfield, Robert C.: The Cardiac Action of the Derivatives of Strophanthidin and Cymarin. *J. Pharmacol. & Exper. Therap.* 70: 338, 1940.

A few derivatives and isomers of strophanthidin and cymarin have been studied in frogs and cats with the aim of determining the relative importance of chemical groupings present in nature.

Strophanthidin is about one-fifth as active in frogs and one-third as active in cats as cymarin, showing that splitting of the sugar, cymarose, results in reduction of action.

Oxidation of the aldehyde group on C<sub>30</sub> of strophanthidin to form strophanthidinic acid is followed by substantial diminution of action—approximately eight times less active in cats, and 153 times less active in frogs, than strophanthidin.

Saturation of the double bond in the side chain is accompanied by practically complete loss of activity as exemplified by dihydrostrophanthidin, dihydrostrophanthidinic acid, and isostrophanthidin. A residual effect may be sometimes demonstrated in sensitive animals, probably due to an intact lactone ring as in the case of dihydrostrophanthidinic acid.

The inertness of the sodium salt of saponified isostrophanthidin may be attributed chiefly to the disappearance of the double bond and lactone ring of the side chain.

Decrease or loss of action may be also suspected if the OH group on C<sub>11</sub> is reacted with another group in the molecule as in the case of pseudostrophanthidin, isostrophanthidin, and the sodium salt of saponified isostrophanthidin.

Very marked reduction or often complete loss of activity may occur when stereochemical rearrangement in the steroid ring system has taken place as illustrated by pseudostrophanthidin, allocymarin, allostrophanthidin, and presumably isostrophanthidin. These results indicate clearly that the digitalis-like action of strophanthidin and cymarin depends on not only a side chain with intact double bond and lactone ring, but also the steroid ring system in favorable spatial isomerism.

AUTHORS.

Allen, C. R., Stutzman, J. W., and Meek, W. J.: The Production of Ventricular Tachycardia by Adrenalin in Cyclopropane Anesthesia. *Anesthesiology* 1: 158, 1941.

At least one action of cyclopropane is to render the dog's heart more irritable to adrenalin by direct stimulation of a brain center above the pons which sends impulses to the heart by way of the sympathetic nerves. The direct action of adrenalin on the heart thus sensitized produces ventricular tachycardia.

AUTHORS.

Parker, Robert L.: Pulmonary Emphysema: A Study of Its Relation to the Heart and Pulmonary Arterial System. *Ann. Int. Med.* 14: 795, 1940.

An anatomic study was made of the heart and pulmonary arterial tree in thirty-two cases of essential emphysema. It was found the emphysema produced enlarge-

ment of the right ventricle in 75 per cent and resultant cardiac failure with decompensation in 44 per cent of the entire group. The severity of emphysema seemed to be closely correlated with the incidence of congestive heart failure as well as to the frequency and extent of right ventricular enlargement. Arteriosclerosis of the pulmonary arterial tree was noted to some degree in 80 per cent of the cases. Arteriosclerotic changes were noted most frequently in the arteries, and narrowing of the arteriolar bed was found in 66 per cent of the total cases studied. The degree of obliteration of the arteriolar bed seemed to be influenced by the severity of emphysema, yet there was no direct correlation between the degree of arteriolar sclerosis and the degree of right ventricular enlargement, nor any relationship between the extent of these pulmonary arteriolar changes and the extent of arteriosclerotic changes in the coronary arteries or the aorta. It was concluded, therefore, that the arteriosclerotic changes of the pulmonary vessels in emphysema represent secondary manifestations of an existent hypertension within the pulmonary circuit which probably is produced by obstruction in the capillary bed. Whereas it is reasonable to assume that when the degree of obstruction in the arteriolar system is great, there is an augmentation of the pulmonary hypertension, it is doubtful that the amount of pulmonary arteriosclerosis seen in the usual case of emphysema produces alone a very marked obstruction to the pulmonary circulation.

AUTHOR.

Smith, Lucian A., Allen, Edgar V., and Craig, Winchell McK.: Time Required for Blood to Flow From the Arm and From the Foot of Man to the Carotid Sinuses. I. Effect of Temperature, Exercise, Increased Intramuscular Tension, Elevation of Limbs and Sympathectomy. *Arch. Surgery* 41: 1366, 1940.

The mean circulation time from the arm to the carotid sinus of normal persons in the present study was twenty and one-tenth seconds. The range was twelve and four-tenths to thirty-three and two-tenths seconds. The mean circulation time from the foot to the carotid sinus was thirty-eight and seven-tenths seconds. The range was twenty-two to sixty-seven seconds.

The temperature of the skin of the extremities has a prominent effect on circulation time from the foot to the carotid sinus and from the arm to the carotid sinus. Warmth of the skin decreases the circulation time, and coldness of the skin increases it.

Exercise of the legs decreases circulation time in the legs.

Elevation of an extremity decreases circulation time in the extremities.

Lumbar sympathectomy decreases circulation time in the legs.

The increase of intramuscular tension caused by strychnine tends to decrease circulation time in the legs.

AUTHORS.

Lund, Curtis J.: The Recognition and Treatment of Fetal Heart Arrhythmias Due to Anoxia. *Am. J. Obst. & Gynec.* 40: 946, 1940.

Impending fetal asphyxia can be determined by careful frequent auscultation during active labor.

A method for continuous auscultation and recording of fetal heart sounds is described.

Fetal heart arrhythmia due to anoxia is described and the response to oxygen recorded.

The etiologic factors of fetal anoxia are discussed.

Early recognition of fetal anoxia and treatment by maternal oxygen therapy will prevent many cases of asphyxia neonatorum.

AUTHOR.

Cutts, Frank B., Clagett, A. Henry, Jr., and Fulton, Frank T.: Smallness or Absence of Initial Positive Deflections in the Precordial Electrocardiogram and Cardiac Infarction. A Study of Patients Who Came to Autopsy. *Arch. Int. Med.* 67: 509, 1941.

In routinely taken electrocardiograms the absence of the initial positive deflection in chest Lead IV F is evidence for the presence of cardiac infarction in the great majority of cases.

An abnormally small initial positive deflection in chest Lead IV F is associated with cardiac infarction in about one-half of the cases in which it is found.

A sharp distinction between abnormal and normal initial positive deflections is impossible in a few cases because of variations found in serial records.

A relatively small, grossly abnormal QRS complex in the precordial electrocardiogram may occur at times and is strong evidence for the presence of cardiac infarction.

In the presence of extreme cardiac enlargement or gross intrathoracic abnormality some caution is indicated in interpreting a small or absent initial positive deflection. An absent or abnormally small initial positive deflection in Lead IV F will rarely occur in the absence of either definite cardiac disease or significant extracardiac abnormality within the chest.

The presence of bundle branch block renders less reliable abnormality of the initial positive deflection or of the S-T interval in the precordial electrocardiogram.

In an interpretation of abnormalities in the initial positive deflection of the chest lead, the deviations of the S-T interval in Lead IV, the clinical history and findings, and the evidence provided by the limb leads should all be carefully considered in every case before a diagnosis is attempted.

AUTHORS.

Evans, Courtenay, and Bourne, Geoffrey: Electrocardiographic Changes After Anoxemia and Exercise in Angina of Effort. *Brit. Heart J.* 3: 69, 1941.

One-third of all cases with angina of effort show no changes in the four lead electrocardiograms.

Nearly half of this group with no cardiographic abnormality give changes suggestive of myocardial disease following anoxemia with 10 per cent oxygen for three to five minutes or after an exercise test.

The abnormal and normal response to anoxemia and exercise are described and discussed.

The exercise test gives an abnormal response slightly more often than the 10 per cent anoxemia test, but changes may occur after anoxemia when none follow after exercise.

AUTHORS.

Wood, Paul: Pulmonary Embolism: Diagnosis by Chest Lead Electrocardiography. *Brit. Heart J.* 3: 21, 1941.

Acute pulmonary embolism may be difficult to distinguish from posterior myocardial infarction, both clinically and by means of limb lead electrocardiograms.

Multiple chest lead cardiograms afford a good method of differential diagnosis.

In posterior myocardial infarction, as is well known, there may be no cardiographic change, or the RS-T segment may be depressed, or the T waves may be very tall.



In pulmonary embolism sufficient to cause right ventricular stress there is sharp inversion of the T wave, maximal and for the longest duration in the right pectoral lead; usually, but for a shorter duration, in the left pectoral lead; and rarely, and for the shortest duration, in Lead IV.

Similar changes may be found in all conditions giving rise to right ventricular stress.

AUTHOR.

**Mortensen, Vagn: The QRS Complex in Precordial Leads in Anterior Wall Infarction. True and False Infarction Curves.** *Am. J. M. Sc.* 201: 349, 1941.

In most clinical works the typical QRS changes in precordial leads in anterior wall infarction are described in terms indicating absence or marked diminution of the R wave; in addition atypical split or W-shaped QRS complexes have been described. The occurrence of a normal QRS complex in IV F in anterior wall infarction has been reported too.

This paper gives a preliminary report on the changes in the QRS complexes in precordial leads in twenty-three clinical cases of anterior wall infarction observed by the writer. In these cases 192 electrocardiograms were taken in the three conventional leads and in two precordial leads, CF<sub>2</sub> and IV F, from a few hours to several years after the acute injury. Twenty of the twenty-three cases showed an initial negative deflection in both CF<sub>2</sub> and IV F, and two other cases showed an initial negative deflection in either CF<sub>2</sub> or IV F in all the records. Therefore this abnormality must be looked upon as a very constant change in anterior wall infarction.

The QRS changes in precordial leads in anterior wall infarction are analyzed, and it is pointed out that these changes are far more characteristic than suggested by previous investigations. It must be considered erroneous to characterize the QRS changes in anterior wall infarction by absence of the R wave, as this explanation covers merely a minor part of the infarction curves (clear-cut central infarction curves), and it is sufficient to characterize the QRS changes in a good many cases, besides being directly misleading in some cases. On the other hand, practically all the QRS changes observed may be analyzed according to common simple rules under the supposition that anterior wall infarction implies two factors, (1) appearance of a Q wave and (2) diminution or complete disappearance of the R wave. The first of these factors is very constant, whereas the other is very variable, giving rise to the many variations in the features of the QRS complex.

The two ways in which a classical ("central") infarction curve may develop from a normal diphasic QRS complex are described (Fig. 2), and the conceptions "true infarction curve" and "false infarction curve" are introduced.

According to the writer's interpretation of the QRS changes in anterior wall infarction, a small initial R wave, which often is reckoned as equal to complete absence of the R wave in connection with anterior wall infarction, represents a considerable deviation from the typical changes. A small initial R wave in a presternal derivation is of no positive significance to the diagnosis of anterior wall infarction, as this abnormality is very common in marked preponderance of the left side of the heart.

The practical result of the view of the QRS changes in precordial leads in clinical cases of anterior wall infarction, as described here, will be that *particular attention must be paid to the presence of an initial negative deflection, with or without absence of the R wave, in the QRS complex in precordial leads.*

AUTHOR.

Blair, H. A., Wedd, A. M., and Young, A. C.: The Relation of the Q-T Interval to the Refractory Period, the Diastolic Interval, the Duration of Contraction, and the Rate of Beating in Heart Muscle. *Am. J. Physiol.* 132: 157, 1941.

In turtle heart strips the electrical activity is recorded from pairs of electrodes, one member of each pair being against the tissue and the other at a distance. The record permits the measurement of the interval between the depolarization and the repolarization of the tissue at a given region. This interval is called the Q-T interval. It is shown to coincide with the absolutely refractory period. It is shortened to one-half or less of its maximal value in a single very early beat. Further slow shortening occurs when the strip is driven for periods at a series of increasing rates. The lengthening of Q-T on slowing the rate is a slower process. Evidence is presented that repolarization arrests the contractile process in the muscle, leading to the conclusion that the electrical processes control the mechanical rather than the mechanical, the electrical. In this connection it is shown that the duration of contraction as measured, for example, from half contraction to half relaxation is related linearly to the Q-T interval over a wide range. In the human heart it is shown that in recovery from exercise there is no fixed relation between the Q-T interval and the rate.

AUTHORS.

Eppinger, Eugene C., Burwell, C. Sidney, and Gross, Robert E.: The Effects of the Patent Ductus Arteriosus on the Circulation. *J. Clin. Investigation* 20: 127, 1941.

Studies of the circulation made on six patients before and after surgical closure of an uncomplicated patent ductus arteriosus show that:

When the ductus arteriosus is open, the blood flow is from the aorta to the pulmonary artery.

There is no flow of blood from pulmonary artery to aorta. Therefore, these patients do not have arterial unsaturation and are not cyanotic.

The volume of blood flowing from aorta to pulmonary artery varied from 4 to 19 liters per minute, which is 45 to 75 per cent of all the blood pumped into the aorta by the left ventricle. These flows occurred in patients with large ducti and under temporary conditions which are known to elevate the output of the heart.

The left ventricle expelled from two to four times the volume of blood expelled by the right ventricle in a given period of time.

Adjustment of the circulation to the patent ductus may be made by an increase in the output of the left ventricle. If this is not sufficient to compensate completely for the leak through the ductus, there may be, in addition, a diminution in the blood flow to the periphery.

Comparable studies in dogs with an artificial aorta-pulmonary artery fistula showed similar circulatory adjustments.

Knowledge of the circulatory changes which occur with patency of the ductus permits a better understanding of the signs and symptoms associated with this condition. Furthermore, these studies of the circulation supply direct evidence of the beneficial effects of operative closure of the ductus in improving the peripheral circulation in some of the patients and in reducing the work of the heart in all of them.

AUTHORS.

Nichols, Charles F.: A Study of Syphilis of the Aorta and Aortic Valve Area. *Ann. Int. Med.* 14: 960, 1940.

A detailed study of seventy cases of syphilitic aortic insufficiency forms the basis of this report. In addition, the pathology of syphilitic aortitis, the diag-

nosis of uncomplicated syphilitic aortitis and an analysis of forty-one cases of syphilitic aortic incompetency which came to autopsy have been presented. Of the seventy cases in the series the ratio of males to females was 6 to 1. Fifty-three of the patients were colored; seventeen were white. The average age was 46.04, with extremes between 28 and 64. The average interval between primary infection and the onset of symptoms was twenty-two years. The most common presenting symptom was dyspnea on exertion, which occurred in 71 per cent. The rarity of paroxysmal dyspnea and pain was noted. An increase in the size of the heart was noted in 93 per cent. The average duration of symptoms before medical attention was sought was ten months, the shortest, two weeks, and the longest five years. Edema of the ankles was present in 40 per cent upon first admission to the hospital. The typical to-and-fro murmur of aortic insufficiency was present in 87 per cent. The presence of a loud musical diastolic murmur and thrill in five patients was discussed and its pathology explained. The average pulse pressure was 84 mm. of mercury. The Wassermann reaction was positive in 85 per cent of the patients. In addition, the appearance on fluoroscopic examination was discussed, and the absence of any noteworthy features in the electrocardiogram stressed. The differential diagnosis between syphilis, rheumatism, hypertension, and atheroma of the aortic valve was considered. The salient points in the clinical course of the disease were discussed, and a possible explanation suggested for the rapid myocardial breakdown.

AUTHOR.

Loewenberg, Samuel A.: A Valuable Sign in the Diagnosis of Functional Aortic Insufficiency. *Ann. Int. Med.* 14: 991, 1940.

In functional aortic insufficiency the systolic pressures in the upper and lower extremities are about equal. In organic aortic insufficiency the systolic pressure in the lower extremity is from 50 to 100 or more mm. of mercury higher than in the upper extremity.

AUTHOR.

Walsh, Bernard J., and Sprague, Howard B.: The Treatment of Congestive Failure in Children With Active Rheumatic Fever. *J. A. M. A.* 116: 560, 1941.

Forty-four children with congestive failure during active rheumatic fever were given various drugs (theobromine calcium-salicylate, theobromine sodium-acetate, theobromine sodium-salicylate, mercupurin, salyrgan and digitalis) for their effect on the heart and circulation.

The xanthine diuretics were found to be of greatest value, in particular theobromine calcium-salicylate or theobromine sodium-acetate in the dose of 1 Gm. three times a day. Theobromine sodium-salicylate given by mouth was found less effective but was useful when given rectally.

Mercurial diuretics given intravenously are effective in producing diuresis but should not be given immediately after full digitalization because of the danger of inducing toxic digitalis reactions during the loss of fluid.

Digitalis proved to be of value, but it was found necessary to use great care in its administration.

AUTHORS.

Perry, C. Bruce: Rheumatic Heart Disease in Identical Twins. *Arch. Dis. Childhood* 15: 177, 1940.

Two pairs of apparently identical twins are described. In the first both children suffered a similar rheumatic attack following a sore throat, which in one only produced scarlet fever. In the second, one child only developed acute

rheumatism and carditis although they had been brought up together. It is concluded that while heredity is of considerable importance in the causation of acute rheumatism, another factor, probably infection, plays an equally, if not more, important role.

AUTHOR.

Thomas, Caroline Bedell, France, Richard, and Reichsman, Franjo: The Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever. *J. A. M. A.* 116: 551, 1941.

Sulfanilamide was given continuously to fifty-five patients with a recent history of acute rheumatic fever during seventy-nine person-seasons between 1936 and 1940. Sixty-seven patients with similar history, who were given no prophylactic treatment, were observed simultaneously during 150 person-seasons.

The drug was taken from November through June, usually in a dose of 1.2 Gm. daily.

No serious toxic effects were observed. Mild cutaneous eruptions and some drop in total white blood cell count without granulocytopenia occurred in a few patients. The leucopenia was self-limited in duration and was of no apparent clinical significance.

Pharyngeal cultures positive for the beta hemolytic streptococcus were less numerous and showed a lower percentage of the organisms among treated patients than among control patients.

While taking sulfanilamide, none of the patients had a major attack of acute rheumatic fever or an acute beta hemolytic streptococcus infection.

Fifteen major attacks of acute rheumatic fever developed among patients not taking sulfanilamide during the control period. One patient, treated during the winter months, had an acute rheumatic recrudescence in August when he was not taking the drug. Five control patients suffered from acute illnesses which might have been of rheumatic character. One control patient was hospitalized with an acute beta hemolytic streptococcus infection.

Subacute bacterial endocarditis developed in two control patients.

Four deaths occurred among the control group, one from acute rheumatic fever and two from subacute bacterial endocarditis. The cause of death in the other case is uncertain. There were no deaths among persons in the treated group.

Sulfanilamide may safely be administered in small daily doses over a long period of time. It appears to be of value in preventing recrudescences of acute rheumatic fever.

AUTHORS.

Seegal, David, and Earle, David P., Jr.: A Consideration of Certain Biologic Differences Between Glomerulonephritis and Rheumatic Fever. *Am. J. Med. Sc.* 201: 528, 1941.

A limited consideration of certain biologic differences between acute glomerulonephritis, chronic glomerulonephritis, and rheumatic fever indicates that:

Although both diseases appear to be initiated by Group A hemolytic streptococcus infection, the geographic incidence of acute glomerulonephritis is similar for all latitude regions in North America, whereas the incidence of rheumatic fever is less frequent in the southern than in the northern latitude regions of North America.

Although twice as many males as females contract glomerulonephritis, this sex variation is not apparent in rheumatic fever.

The preceding clinical infection in acute glomerulonephritis is a "deep" hemolytic streptococcus infection in at least two-thirds of the cases, in contrast to the usual superficial pharyngitis preceding the onset of rheumatic fever.

There is a distinct shortening of the latent period following infection in the exacerbation of chronic nephritis as compared with that in acute glomerulonephritis. This shortening of the latent period in exacerbation or relapse is absent in rheumatic fever.

Relapse, while a rarity following the healed state of acute glomerulonephritis, is a common if not regular occurrence following the rheumatic episode.

AUTHORS.

Farquhar, Lucille R., and Paul, John R.: *Rheumatic Fever in New Haven, Conn. A Survey of Recent Hospital Admissions.* Public Health Reports 55: 1903, 1940.

Data relative to rheumatic fever have been collected from all of the three general hospitals in the city of New Haven, Conn., and from these data estimates have been made on the annual number of active and inactive cases of rheumatic fever admitted to these institutions.

The average number of hospitalized cases of active rheumatic fever in the city of New Haven is 40 per year (an annual case rate of 29 per 100,000).

The active cases make up 1.2 per cent of the admissions to the medical services of local hospitals, and the inactive rheumatic heart disease cases make up an additional 1.5 per cent of these admissions.

From the standpoint of total admissions to the medical service of the New Haven Hospital this disease occupies a position of numerical importance which is greater than that of other acute infectious diseases, such as poliomyelitis, scarlet fever, measles, pertussis, and diphtheria, but less than that of the two major chronic infectious diseases, tuberculosis and syphilis.

We now have two rough measures of the prevalence and of the severity of this disease in this community. Their relative significance can be best appreciated when comparisons are eventually available from other localities.

AUTHORS.

Sheehan, H. L., and Sutherland, A. M.: *The Pathology of Heart Disease in Pregnancy.* J. Obst. & Gynaec. Brit. Emp. 47: 597, 1940.

An analysis was made of the clinical and pathologic findings in 108 obstetric patients who showed acute or chronic lesions of the heart valves at autopsy. For purposes of control these were compared with the autopsy findings in 215 women of child-bearing age who were not pregnant and who had similar valve lesions, and in 705 obstetric patients with normal valves. The following conclusions were drawn:

Chronic rheumatic valvular disease is present in 1.5 per cent of all obstetric patients in this locality. The mitral and aortic valves are involved with about the same frequency as in women not pregnant, but tricuspid lesions are found at autopsy much less commonly than in women not pregnant. The clinical diagnosis of particular chronic valve lesions is much better when heart symptoms are present than when they are not present, but a correct diagnosis is made in less than half of the cases. The difficulties in clinical diagnosis make it impossible to place full reliance on studies based on clinical data alone.

The mortality in women with chronic valve lesions was 6.3 per cent; 0.9 being due to superimposed ulcerative endocarditis, 2.9 per cent to other cardiac causes, and 2.5 per cent to noncardiac complications.

Nearly half the patients had had some evidence of congestive failure which usually began either in the first few weeks of pregnancy or at about six months. This was related to the type of valve lesion, severe mitral stenosis and mitral stenosis combined with aortic stenosis being the most serious, while incompetence of valves

The syndrome usually called "coronary occlusion," which consists of prolonged subexternal oppression or pain, a fall in blood pressure, pallor and the other manifestations of shock, and is accompanied by electrocardiographic changes, fever, leucocytosis and an increased sedimentation rate, in reality signifies myocardial infarction and should be so termed.

In all three of the discussed syndromes, i.e., angina pectoris, coronary failure and acute myocardial infarction, the underlying mechanism seems to be a relative disproportion between the requirements of the heart for blood and the supply through the coronary arteries. The changes in the myocardium resulting from this disproportion depend solely on the extent and duration of the relative ischemia, not on the manner in which they are produced.

The absolute necessity for immediate and complete bed rest, sedation, reduction of excessively high cardiac rates, and other measures designed to reduce the work of the heart in the presence of prolonged cardiac pain is emphasized as a means of limiting the extent of myocardial necrosis or even preventing its development. Such a regimen also affords an opportunity for the development of a more adequate collateral circulation.

#### AUTHORS.

Gouley, Benjamin A., and Anderson, Edward: Chronic Dissecting Aneurysm of the Aorta, Stimulating Syphilitic Cardiovascular Disease; Notes on the Associated Aortic Murmurs. *Ann. Int. Med.* 11: 978, 1910.

Occasional cases of dissecting aortic aneurysm of the chronic type closely simulate hectic cardiovascular disease. Such patients present the signs of aortic valvular regurgitation and of aortitis. Progressive cardiac decompensation may continue for many months or even years. There is often no pain and no history of a painful attack, so that if it had been present it was relatively slight and soon forgotten. Life is terminated by heart failure, or occasionally by a long delayed secondary aortic rupture.

The aortic valvular leakage is directly dependent on the proximity of the dissection to the valvular ring. The dilatation of the latter and of the ascending arch of the aorta in the chronic cases suggests a loss of tonus possibly secondary to the destruction of some controlling mechanism. A "mechanical" noninfectious deformity of the aortic leaflets may result from long-continued inefficient closure of the aortic valve.

Notable clinical features were: (1) the persistently negative serologic tests for syphilis in the large majority; (2) the usually marked and often enormous enlargement of the heart, especially of the left ventricle and the constant dilatation of the ascending arch of the aorta; (3) the relatively high incidence of hemiplegias in cases of chronic dissecting aneurysm showing signs of aortic regurgitation.

#### AUTHORS.

Whittenberger, James L., and Higgins, Charles: Ligation of the Inferior Vena Cava. *Arch. Surgery* 41: 1334, 1910.

Ligation of the vena cava above both renal veins causes death in a few hours from surgical shock due to accumulation of blood from two kidneys, in the posterior portion of the body. When oblique ligation of the vena cava between the kidneys is done, allowing development of collateral veins in one kidney, subsequent complete high ligation of the vena cava is well borne; it is not followed by shock or interference with renal function in the kidney with adequate venous drainage.

#### AUTHORS.

The electrocardiogram of acute coronary insufficiency with infarction is characterized by the presence of a depressed RS-T segment and flattening or inversion of the T wave in two or more leads. The occurrence of an elevated RS-T segment or a Q wave, particularly in Lead I, is rare. The electrocardiogram thus differs from that of acute coronary occlusion in which the latter changes are common. The presence of a depressed RS-T segment in acute coronary insufficiency is attributed to the subendocardial localization of the infarction.

AUTHORS.

Koucky, John J., Beck, William C., and Hoffman, John M.: *Peripheral Arterial Embolism*. *Ann. J. Surg.* 50: 39, 1940.

Acute arterial embolism of the extremities is a complication of other disease. It therefore adds the mortality of the embolism to the mortality of the pre-existing lesion. Embolectomy should be carried out in favorable cases, within six hours of the onset. Conservative measures may be of benefit and may save the extremity as there is a diffuse vasospasm accompanying the lodgment of the embolus. Amputation must, however, be done in a large percentage of the cases. There is a "time of election" for the amputation, viz., when the patient's general status has been improved, and before the toxemia has developed. An amputation which does not open up new fascial spaces is one of choice.

AUTHORS.

Blumgart, Hermann L., Schlesinger, Monroe J., and Zoll, Paul M.: *Angina Pectoris, Coronary Failure and Acute Myocardial Infarction*. *J. A. M. A.* 116: 91, 1941.

A detailed clinical and pathologic study of 355 consecutive cases examined post mortem has been made with particular reference to the role of coronary occlusions and the collateral circulation in angina pectoris, coronary failure, and acute myocardial infarction. In normal hearts intercoronary anastomoses larger than 40 microns are generally absent. Fine communications measuring less than 40 microns in diameter can be demonstrated by the injection of watery solutions but are probably of little functional significance in obviating the untoward effects of sudden coronary narrowing or occlusion. Complete occlusion or considerable narrowing of one or more coronary arteries may exist without giving rise to any clinical signs or symptoms and without having produced myocardial damage. The apparent inconsistency between the presence of long standing obstructive arterial lesions and the absence of significant pathologic or clinical evidence of myocardial damage was dispelled by the demonstration of a collateral circulation which served as a bypass in relation to the obstruction in each of these hearts. Every patient suffering primarily from angina pectoris without evidence of valvular disease or arterial hypertension has shown old complete occlusion of at least one major coronary artery at post-mortem examination; in the majority of instances at least two of the three main coronary arteries had been occluded before the terminal illness. Attacks of cardiac pain more prolonged than those of angina pectoris but unattended by evidence of myocardial infarction are more accurately described as attacks of coronary failure. A comparative study of the clinical characteristics of coronary thrombosis and those of myocardial infarction forces the conclusion that coronary thrombosis and occlusion, per se, do not necessarily produce any characteristic clinical manifestations.

statistical delineation of build types and the exclusive reliance upon mean and modal pressures, instead of a study of the incidence of low and high pressure distribution and the actual to expected ratio.

The incidence of tall men and women decreased steadily with an increase in age. This is an unusual and striking phenomenon, and is probably due chiefly to a high mortality of tall persons in earlier age groups. In a random group of mixed builds and weights short men and women will show higher mean and modal systolic and diastolic blood pressures than tall men and women. Short men and women showed a higher incidence of high pressures than tall men and women. When the build groups are separated and held constant, a marked difference in blood pressure is noted between tall and short persons and is reversed to the height relationship mentioned above. The tall lateral or broad person is more susceptible to hypertension than the short lateral one and is less likely to have a low pressure. Tall lateral or broad men show an actual to expected ratio of about two and one-half times as many systolic and diastolic hypertensives as short lateral men. Tall lateral women show twice as many systolic and diastolic hypertensives as short lateral women. Tall lateral men have a slightly smaller incidence of low pressure than short lateral men. The actual to expected ratio shows that among linear or thin men the tall men have only one-half as many low systolic and diastolic pressures as the short men. The actual to expected ratio shows no difference between the short and tall linear or thin women of low and high pressures. In a previous paper it was shown that the lateral or broad build person in any height group carried the highest incidence of hypertension. In this paper it is shown that lateral build is most often found among short men and women. This unequal distribution of lateral build in short and tall persons explains the discrepancy mentioned. Although the tall person carries a greater hazard of hypertension than any other person, the larger number of lateral builds among short persons causes the bulk of the hypertensive population to be found among short persons. The short person shows a higher incidence of hypertension than the tall one in any weight group. There are, therefore, three influencing height factors in hypertension. First, there is the difference in blood pressure between tall and short persons in specific build groups. This is purely a height difference. Second, there is the difference in pressure between tall and short persons when weight is held constant. Third, there is the difference in pressure between short and tall persons in any total group in which build and weight are naturally mixed. The second and third height differences are dependent upon the build factor.

AUTHOR.

Master, Arthur M., Gubner, Richard, Dack, Simon, and Jaffe, Harry L.: *Differentiation of Acute Coronary Insufficiency With Myocardial Infarctions From Coronary Occlusion*. Arch. Int. Med. 67: 647, 1941.

A clinical and electrocardiographic study was made of forty-eight cases of acute coronary insufficiency, i.e., recent myocardial without acute coronary occlusion. The myocardial following coronary insufficiency differs, as a rule, from that following coronary occlusion by its focal and disseminated character and its localization in the subendocardium and papillary muscles of the left ventricle. Clinically, coronary insufficiency is usually associated with some factor which increases the work of the heart or diminishes the coronary flow, most often in a subject with antecedent cardiac enlargement and coronary atherosclerosis. The precipitating factors in the series studied included: heart failure; shock due to operation, pulmonary embolism, acute hemorrhage, and infection; marked tachycardia or bradycardia; acute anemia; aortic valve disease; and hypertensive crises.



was of less significance. The degree of hypertrophy of the heart did not appear to

be a factor of importance in causing decompensation.

Deaths during or immediately after labor are usually not due to the progressive exhaustion of a badly decompensated heart, but are in most cases catastrophic acute heart failures in patients who have been either not or only slightly decompensated. Such acute heart failures are not satisfactorily described as acute pulmonary edema, because the lungs are edematous at autopsy in nearly all patients suffering from heart disease, whatever the manner of death.

The deaths during pregnancy or the late puerperium are several times as common as in patients not pregnant.

While many patients have never had congestive failure before, any patient whose heart becomes decompensated in a pregnancy will almost inevitably have the same condition in every subsequent pregnancy.

The American Heart Association is of some value when it is based on the patient's condition in the last quarter of pregnancy, but it is not of help in assessing the prognosis before this stage of pregnancy.

The common belief that decompensation of the heart is related to a myocarditis or acute pancreatitis does not rest on a satisfactory basis. On the other hand, simple recurrent endocarditis superimposed on old chronic valve lesions shows a very much higher incidence in pregnant women than in those not pregnant, and in those whose heart is decompensated than in those in whom it is not. The reason for the very high incidence in obstetric cases is not clear, but the recurrence appears to develop in the course of pregnancy and not in the puerperium. Recurrent endocarditis cannot be diagnosed satisfactorily during life except by inference. Though its exact significance remains to be established, it is an important complication of chronic valve lesions.

Simple acute endocarditis occurs in pregnancy with about the same frequency as in women not pregnant, and does not present any special features. Ulcerative endocarditis superimposed on old chronic valve lesions and subacute bacterial endocarditis are rather commoner in pregnant women than in those not pregnant. These conditions develop during the course of pregnancy and not in the puerperium. They may be based on recurrent endocarditis. They lead to a particularly severe type of decompensation.

Primary ulcerative endocarditis (without previous chronic valve lesion) is very much less common in pregnant women than in women not pregnant. It appears from the literature that an ulcerative endocarditis developing in the puerperium was very common in the preantiseptic days of obstetrics, but this type of valve lesion does not seem to occur nowadays. A patient who has any kind of valve lesion, chronic, recurrent, acute, or ulcerative, may also have pyelonephritis, hypertensive toxemia, eclampsia, or puerperal sepsis, but these diseases do not have any relation to the valve lesion, either as cause or effect. Deaths associated with congenital heart disease, cardiac neurosis, or syphilis or primary sclerosis of the aortic valve are rare.

AUTHORS.

Robinson, Samuel C.: Hypertension in Relation to Height. J. Lab. & Clin. Med. 26: 930, 1941.

A gross anthropologic study of 2,552 men and 2,021 women shows for the first time in medical literature the positive correlation of height to blood pressure. Literature shows that no study, thus far, has found the height difference as reported in this paper. An explanation for this failure is probably due to a lack of correct

deTakáts, Géza, and Scupham, George W.: *Revascularization of the Ischemic Kidney*. *Arch. Surgery* 41: 1394, 1940.

Four hypertensive patients in whose cases the diagnosis of malignant nephrosclerosis was made were operated on with the idea that the ischemic kidney might obtain some additional circulation. The kidneys were decapsulated; the cortex was incised and the omentum or a pedicled muscle flap was wrapped around the kidney. The four case reports are summarized. One patient has been followed for three and one-half years. In no patient was there a definite improvement. It is possible that if patients with essential hypertension with earlier or more proximal vascular damage were subjected to such a procedure the condition might be arrested or improved. The importance of taking renal biopsy specimens and the difficult interpretation of biopsy observations in the early stages are emphasized. For the late stages in which the patient is referred to the surgeon, renal vascularization has been of no value.

AUTHORS.

Matas, Rudolph: *Personal Experiences in Vascular Surgery*. *Ann. Surg.* 112: 802, 1940.

In a historical preface the author traces in a most interesting way, the development of surgery of blood vessels, especially at the Charity Hospital in New Orleans. This is an interesting chapter in medical history. In regard to the author's personal experiences he states that, "my internship in a hospital where the surgery of the blood vessels had become a proud historic tradition, my association with the great surgeons and teachers just mentioned, who were especially concerned with the cure of aneurysm, and the anatomic experience that I had acquired early in my career as demonstrator of anatomy for over ten years in the dissecting rooms of the medical school, all combined to give me a special interest in vascular pathology and thereby to utilize the unusual opportunity given me to study, clinically and surgically, the ever fascinating problems that for practically 60 years have presented themselves to me as a visiting surgeon of the Charity Hospital and of the other local institutions with which I have been associated."

In a separate section the author describes briefly the development of his special operation "endo-aneurysmorrhaphy."

The larger portion of the paper is devoted to a classified summary of 620 operations upon the blood vessels performed for all causes between the years 1888 and 1940. This summary is in a statistical manner and describes first the anatomic distribution of the operations, second the regional classification in detail with results of the carotid vessels, and third a summary of procedures employed in the operations.

There is included a chronologic bibliography of contributions to vascular surgery by the author.

McCULLOCH.

Matas, Rudolph: *Aneurysm of the Abdominal Aorta at Its Bifurcation into the Common Iliac Arteries. A Pictorial Supplement Illustrating the History of Corrine D., Previously Reported as the First Recorded Instance of Cure of an Aneurysm of the Abdominal Aorta by Ligation*. *Ann. Surg.* 112: 909, 1940.

Among the more salient conclusions that may be drawn from the clinical and post-mortem studies of the case are:

The patient died 17 months and 9 days after the ligation of the abdominal aorta for a leaking (ruptured) syphilitic aneurysm of the abdominal aorta at the bifurcation, including both common iliac arteries.

The cause of death was tuberculosis—a cause unrelated to the aneurysm.

That the collateral circulation *above and below the aneurysm* was well established before the ligation of the aorta.

That the patient had been clinically cured of the aneurysm, and that this had ceased to be an active factor in her invalidism fully three months before her death.

The clinical evidence of cure was fully confirmed at the post mortem by the complete consolidation, contraction of sac contents, and beginning organization of the clot.

The invalidism and general disabilities, that hospitalized the patient until her death, were caused by the ravages of a disseminated widespread pulmonary, lymphatic, and joint tuberculosis, which flourished with unusual rapidity and luxuriance in a soil seemingly fertilized by a saturating and malignant luetic infection.

The aorta was totally occluded for 9 days following the ligation, during which all pulsation ceased and the peripheral pulses in the femoral and pedal arteries were suppressed.

During this period of total occlusion, the patient remained in a critical condition from threatened cardiac and pulmonary failure (passive congestion, patchy lobular pneumonia, pulmonary edema), which was relieved only by the yielding of the ligatures sufficiently to allow a small, reduced stream to flow through the ligated segment, thus converting a total atresia into a partial, stenotic occlusion.

The yielding or relaxation of the ligatures was not caused by any slipping of the knots, but as demonstrated at autopsy, by the soaking of the cotton fibers in the tissue juices, and the permeation and erosion of the fibers by giant foreign body cells.

The reduction of the aortic stream to about one-tenth or one-eighth of the caliber of the normal aorta was conducive to the final cure of the aneurysm by favoring a gradual deposition of clot and consolidation of the aneurysmal sac.

The anatomic and histologic studies of the aorta at the seat of the ligation showed, conclusively, that the cotton tape ligatures employed in this case (tightened without crushing force) were well tolerated by the tissues and caused no damage to the artery.

As shown in Figs. 7-11, the two one-half inch cotton tapes remained imbedded and incorporated in the aortic walls as a constricting ring for over 17 months without causing the slightest ulcerative, necrotic or thrombotic changes in the arterial coats and especially the intima which remained well-lined and polished with normal endothelium.

This experience shows that a partial occlusion can cure an aneurysm of the terminal aorta slowly, but with greater safety than an immediately total occlusion, without cutting through the artery or causing ulcerative alterations in the intima that might lead to hemorrhage or thrombosis.

It would seem that in large and leaking aortic aneurysms, with progressive sub-peritoneal extravasation, the collateral circulation is well established. In such cases the immediate total occlusion, which is especially indicated to stop leaking, may probably be better tolerated than in the earlier and nonleaking aneurysms, in which the collateral circulation has not had time to develop.

In view of the fact that sterile cotton tape is so well tolerated by the tissues and is ultimately incorporated by the aorta in the structure of its walls, it would seem unnecessary, and superfluous, to resort to extemporized autogenous fascial strips or to heterogeneous aponeurotic or other membranous strips, kept in stock, when the cotton tape will answer the same purpose with greater simplicity and safety.

Judging by the recent experimental evidence and the increasing number of clinical cures of aortic aneurysms by ligation and by suture methods, and the interesting evidence recently furnished by the laboratory, it would seem reasonable to expect that the great desideratum of abdominal aortic surgery, namely, the safe occlusion of

the aorta in any part of its abdominal and low thoracic course, by gradual methods of occlusion (Owings) will ultimately become as feasible and legitimate in the surgical clinic as in the experimental laboratory.

AUTHOR.

Behneman, H. M. F.: Should Coronary Disease and Hypertension be a Cause of Rejection in Industry? *J. A. M. A.* 116: 209, 1941.

Augmented work increases oxygen consumption. When the entire heart is confronted with a general lack of oxygen, the result is the picture of congestive failure; when there is a local lack of oxygen in the myocardium the result is angina pectoris, if mild, and infarction, if severe. The normal heart is usually able to meet the load placed on it by industry; there are a few exceptions. Persons with abnormal hearts, circulatory hypertension, and vascular diseases sometimes fulfill the demands made on them for a lifetime of activity but more often tend to fail eventually from even the routine activities and frequently fail when extraordinary activity is demanded. The presence of systemic disease is detrimental to normal circulatory function. Cardiac failure is in direct ratio to oxygen want. Exertion, disease, and emotional states cause hypertension, which is usually a forerunner of coronary disease. The mechanism of production of coronary disease and hypertension has been reviewed in the light of their relation to industry.

Industry should reject workers with coronary disease and hypertension only when the work contemplated is clearly destined to exceed their ability to respond normally. Industry should accept responsibility for the pathologic conditions it has created or exacerbated. Industry and unions should cooperate by allotting work within the ability of the worker with heart disease, because 70 per cent of those rejected are able to work at something. Differentiation between ordinary and extraordinary activity is difficult but possible.

In conclusion I offer the following thoughts toward solution of this controversial subject:

Institute pre-employment examinations with the right of the worker to sign a waiver which the law will recognize, thus acquitting the worker with his disabilities while protecting the employer.

In cases of questionable liability for cardiac disorders arising out of employment, demand careful medical analysis of each case by a competent examiner, who will painstakingly start his investigation not just from the time of onset of apparent disability but from a period many days previous thereto.

Establish wider use of electrocardiography, the value of which often exceeds that of the widely used roentgenography.

Amend the present industrial laws to allow finer gradations and degrees of incapacity.

Abolish the unfair laws extant in many states where a worker's death gives dependents full award when death has been due only to exacerbation of admitted, pre-existing disease. Industry should rightfully reject a claim for full death benefits in the rupturing of an old syphilitic aneurysm at work which would have ruptured soon without any exertion; at present there is little or no allocation of degree of responsibility. In California now the award is \$6,000 net.

Give the disabled worker prompt and proper medical care; rehabilitate him. Do not discard him, but develop him, and work with placement and rehabilitation bureaus which find work for disabled persons in skilled and unskilled labor.

Define more clearly in each state which occupational diseases are compensable and to what degree. As proposed by Robert T. Legge, create legislation enabling the person with heart disease to work under medical supervision yet releasing the employer and insurance carrier from financial liability in case of death.

At present, expert medical testimony is in a deplorable state. Create and define standards of qualification and urge their acceptance by commissions and courts.

Teach more industrial medicine in the nation's medical schools.

Create state medical boards of review which should decide which cases are worthy of consideration by commissions and courts. Such boards would eliminate many evils of the present system of decisions by lay referees, whose intentions are often buried in a mass of conflicting medical testimony.

Lastly, the principals must get together; the worker, the union, the employer, the insurer, and the physician all have something to learn from one another.

That is my answer to the question before me. It cannot be a sweeping, conclusive one because it depends on the merits of the worker in each individual case.

This answer is a challenge to the industrial physician, especially when, with the vast defense program of the United States imminent, there will soon be a chance to place every available person. It is one I know will be met successfully to provide another brilliant chapter in the annals of American medicine.

AUTHOR.

Murphy, Francis D., Correll, Howard, and Grill, John C.: *The Effects of Intravenous Solutions on Patients With and Without Cardiovascular Defects*. J. A. M. A. 116: 104, 1941.

No tests of cardiovascular function, so far known, will enable us to determine beforehand that the patient will respond unfavorably to fluids administered intravenously.

Careful clinical examination to determine the presence or absence of heart disease is still the best preventive for unfavorable reactions to fluid.

In the presence of heart disease, regardless of the state of compensation, fluids must be given slowly, in small volumes, preferably isotonic and repeated at intervals of not less than four to six hours.

These tests of cardiovascular function showed a few constant changes even with the precipitation of heart failure.

Fifty per cent dextrose solution, with or without 8 grains (0.5 Gm.) of aminophyllin, in volumes of 100 c.c. or more, at rates of 10 c.c. a minute, are extremely dangerous when used in treatment of heart failure, making from 50 to 100 per cent of the patients worse and precipitating failure in 20 per cent of grade 3 cardiac patients.

The danger of fluid injection in cardiac patients may not be in increasing blood volume per se but rather in further altering the already disturbed chemistry of the body fluid, thus increasing osmotic pressure derangements.

The ultimate fate and mode of distribution or loss of injected fluid is dependent on the kind and concentration of the solution, state of hydration of the patient, degree of cardiac compensation, level of venous pressure, and chemistry of body tissues influencing osmotic pressure.

Physiologic solution of sodium chloride may prove more useful in increasing blood volume than hypertonic solutions.

Noncardiac patients in the older age groups tolerated fluids as a substitution therapy, in amounts up to at least 3,000 c.c. daily in 1,000 c.c. doses at rates of from 20 to 40 c.c. per minute, even in the absence of dehydration.

Alteration of dextrose with the physiologic solution of sodium chloride obviated the changes in blood dilution, weight gain and occult or visible edema occurring with physiologic solution of sodium chloride alone.

The indiscriminate use of intravenous fluids, especially for persons with any cardiovascular defect, should be discouraged and the safeguards suggested be more strictly adhered to.

AUTHORS.

**Morris, Noah, and Rogen, Alfred S.: Effect of Calcium on Diuresis in Cardiac Decompensation. *Lancet* 2: 515, 1940.**

Calcium gluconate was administered intravenously to ten patients with cardiac edema. It had little immediate effect on the urinary output. In six out of seven patients who had previously been receiving digitalis the diuretic effect of this drug was increased when given after a course of injections of calcium gluconate. In nine out of ten patients with cardiac edema injections of parathyroid hormone enhanced the diuretic action of mersalyl and digitalis.

AUTHORS.

**Cohen, Robert V., and Brodsky, Maurice L.: Allergy to Digitalis. *J. Allergy*. 12: 69, 1940.**

The findings in a case of allergy to digitalis are reported. The patient exhibited the cardinal symptoms of an allergic drug response, i.e., fever, pruritus, urticaria, joint involvement, and edema of the face. Symptoms occurred only after the ingestion of the drug and were of short duration. During the days when the patient received no digitalis, there were no allergic manifestations. No other medication was taken during this period. When the digitalis was again administered the same symptoms reappeared. Since final cessation of digitalis administration, there have been no further allergic manifestations.

The negative skin tests obtained in this case are compatible with the diagnosis of digitalis allergy, since negative reactions are usually obtained in cases of drug allergy. The latter diagnosis depends largely upon the history, objective findings, and the results of the administration and withdrawal of the suspected agent. It is worthy of note that, following the first dose of digitalis, allergic manifestations appeared within thirty minutes. The patient already had an allergy to digitalis, either natural, or acquired.

AUTHORS.

## Book Reviews

CALIBRATED PHONOCARDIOGRAPHY AND ELECTROCARDIOGRAPHY. A CLINICAL-STATISTICAL STUDY OF NORMAL CHILDREN AND CHILDREN WITH CONGENITAL HEART DISEASE: By Edgar Mannheimer, M.D. Acta Paediatrica, Vol. XXVIII, Suppl. II, Stockholm, 1940, 287 pages, 59 illustrations.

The author of this monograph has attempted a very difficult piece of research. He has tried to analyze the complex noises produced by the heart in a fashion similar to spectroscopic analysis of light, and to discover the energy recorded in six frequency bands, namely, below 100 cycles per second, 50 to 175 cycles, 100 to 250 cycles, 175 to 400 cycles, 250 to 500 cycles, and 500 to 1,000 cycles. This he has studied in 135 normal children from infancy to the age of 14 years, and in ninety children with congenital heart disease from "0 years of age to puberty." These groups were also investigated electrocardiographically.

Sound and electrocardiographic tracings were obtained with a complicated phonocardiograph which permitted simultaneous recording of the heart sounds and electrocardiogram. No simultaneous sphygmographic tracings were made; this imposes a serious limitation to the analysis of diastolic phenomena. Filters were introduced to permit the passage of the frequency bands mentioned and thus produce a crude sound spectrum. Energy, as recorded by the amplitude of the waves, was calibrated against vibrations produced by constant frequency oscillators of known voltage whose frequencies were 70, 175, 275, 375, and 700 cycles per second. An extensive review of the literature precedes the experimental work and should be useful for reference, for the bibliography contains 192 titles.

There are four divisions of the study, namely, (1) heart sound records of normal children, (2) electrocardiograms of normal children, (3) heart sound records of children with congenital heart disease, and (4) electrocardiograms of children with congenital heart disease. Brief comment may be made concerning each group.

1. *Heart Sound Records of 135 Normal Children.*—An effort was made to exclude all children with cardiac lesions or with a history of rheumatic infection. The first, second, and third sounds and auricular sounds and murmurs were analyzed as to frequency, amplitude, duration, and relation to the electrocardiogram. In this, as in the rest of the studies, the statistics were submitted to the most minute mathematical analysis—a refinement which impresses the reviewer as not fully justified by the data, largely because of the variables introduced by differences in chest wall thickness and resonance, and inevitable variations in microphone application pressure. The author found that these factors were pronounced in the lowest frequency ranges, which, of course, have the greatest energy components. He confirms the work of others in finding "that the heart sounds are, throughout, characterized by big, irregular vibrations of a high amplitude and a low frequency." A systolic murmur was recorded in three-fourths of these normal subjects. The dilemma of investigators of this phenomenon appears in this sentence: "Even when the amplitude of the murmur has been given as naught, a certain suggestion of rippling, has, as a rule, been noticeable during systole." To the reviewer, this suggests the inadvisability of using the term "murmur" to include inaudible vibrations, and the author found that this systolic "murmur" was, as a rule, imperceptible to auscultation. This does not, however, disprove the fact that normal ventricular systole is accompanied by inaudible and, at times, audible vibra-

tions. "Still, on examination, it is found that no significant difference exists as to frequency and amplitude between perceptible and imperceptible murmurs." The subjects were examined at the base and apex of the heart, erect and supine, and before and after exertion. The amplitude of the first heart sound was higher in the erect position and after work. A third heart sound was recorded in about 70 per cent of the cases, and in six of seventeen infants under 1 year of age. The auricular sound was found in 50 per cent of the cases; it had a fundamental frequency of about thirty, and was not heard on auscultation because of the absence of overtones.

2. *Electrocardiograms of Normal Children.*—One hundred eighteen subjects, between the ages of 2 and 14 years, were studied. Great variations were found, and the means of the figures were not significant. The mean of the P-R interval was 0.15 second, but he regards conduction as abnormal only when the time is in the neighborhood of 0.20 second. Sex differences found by others were not confirmed nor considered statistically significant. Not rarely,  $Q_3$  had an amplitude exceeding 25 per cent of the maximum QRS amplitude. The Q waves in Leads I and III decrease through childhood; they are greatest at the age of 3 years.  $T_2$  was negative in 19.5 per cent. A tendency to right axis deviation was found between 3 and 13 years of age, and right axis deviation should not be considered pathologic below 110 to 120 degrees. The amplitude of the chest lead is higher in children and decreases with age.

3. *Heart Sound Records of Children With Congenital Heart Disease.*—Although a large amount of data has been collected in this study of ninety patients, its value is questionable. This is largely because the author was obliged to forego any attempt to diagnose the specific defect, except in six autopsy cases. Of the whole group, twelve were cyanotic and sixty-eight were not. Records appeared to show that the first heart sound had a larger than normal amplitude within the frequency bands of under 100 cycles, and between 50 and 175 cycles. The second heart sound also showed a larger amplitude. The third heart sound was less common than in normal persons, but the auricular sound showed no significant average difference from normal. The systolic murmur was larger in amplitude. In the band of 50 to 500 cycles this murmur was recorded in 90 per cent of the cases and appeared to have a higher pitch than the normal systolic murmur. Ten patients had the continuous murmur of patent ductus arteriosus. In most cases it was of high amplitude.

4. *The Electrocardiograms of Children With Congenital Heart Disease.*—One hundred thirty-five patients, from birth to puberty, were included. Twenty-five were studied post mortem; fifteen were cyanotic, and ten were not. The conclusion is reached that "generally speaking, special diagnosis cannot in the individual case be based on the electrocardiogram." He confirms a previous observation of Scham that the form of the electrocardiogram is not always consistent with what is found at autopsy, especially with reference to axis deviation and ventricular hypertrophy. He suggests that this is to be explained as a result of conduction defects within the ventricles. In morbus caeruleus, large P waves and right axis deviation are the most important abnormalities. In noncyanotic patients the electrocardiogram is not rarely perfectly normal. Atypical, diphasic QRS complexes are the most characteristic changes. In certain cases, high amplitude of the QRS, with right or left axis deviation, may be found. In contrast with the electrocardiogram in acquired heart disease, that in congenital heart disease retains a consistent pattern when repeated on the same child. Exceptions to this are found in infancy.

In comparing auscultation with phonocardiographic records, the author found twenty-three tracings outside the normal as regards the four heart sounds, and only one of these was considered abnormal with the stethoscope; it was an accen-



tuated first sound. The second sound was considered accentuated on auscultation in thirty-two cases, whereas the sound tracing recorded only eleven. No gallop rhythms were diagnosed clinically, but the sound record was regarded as showing a few with pathologically increased third sounds and auricular sounds.

The reviewer agrees with the author that "future experience will decide the utility of the method with regard to cases of suspected congenital or acquired heart disease." The problem of calibrating heart sounds and murmurs in an objective manner has appealed, no doubt, to most workers in the field, but this solution assumes that such phenomena, as recorded from the chest wall, have a validity, and a relation to the same vibrations in the heart, which do not exist in such a simple quantitative ratio. Mannheim's figures seem to show that a thick chest wall or breast tissue reduces the amplitude only in the lower frequency ranges, but so does firmer application of the chest piece, by altering the natural period of the skin diaphragm bounded by it. It is hard to reproduce sound records identically, even in the same person on successive trials.

The technical design of the instrument is excellent. However, arbitrary division of the recording into the frequency bands studied introduces a spurious simplification into a very intricate problem, a problem which can only be solved eventually by division into much narrower frequency ranges, thus giving records susceptible of harmonic analysis.

This monograph should, however, help to remove some of the misconceptions about the role of heart sound records and also to clarify the confusion in the minds of some concerning intensity of sound (which is being measured) and loudness, which is a subjective sensation. In graphic records we are searching for objectivity, and what we see in a sound tracing cannot reproduce what we hear, although this can be approached by logarithmic recording.

We need more of Mannheim's type of work, even though his goal may not be attainable, nor, at the moment, have any practical significance. To the reviewer, the recording of a sound spectrum appears more likely to be of importance as a qualitative rather than a quantitative measure. Undoubtedly, the rapid refinement of electrical methods will give us increasingly valuable information.

HOWARD B. SPRAGUE.

**ELECTROCARDIOGRAPHY IN PRACTICE:** By Ashton Graybiel, M.D., Instructor in Medicine, Harvard Medical School, and Paul D. White, M.D., Lecturer in Medicine, Harvard Medical School. W. B. Saunders Co., Philadelphia, 1941, 319 pages, 272 illustrations, \$6.00.

All who, for the first time, have read a textbook on clinical electrocardiography, or who have taken a course in this subject, have felt the need for a large collection of records abundantly illustrating both the more common and the rarer deviations from the normal. Such a collection of records can be studied at leisure for practice in electrocardiographic interpretation, and may be used as a sort of pictorial encyclopedia when abnormalities of an unfamiliar kind are encountered. This work, in which some 270 electrocardiograms of all varieties are reproduced, meets this need in an entirely satisfactory manner. All of the tracings are beautifully reproduced, and, in all except a few instances, Lead IV F, taken according to the recommendations of the Committee on Precordial Leads of the American Heart Association, is reproduced below the three standard limb leads. The first 140 records are arranged according to diagnosis; the last 130, which are intended for practice in interpretation, are in random order. An excellent analytic index is supplied.

The reviewer does not hesitate to recommend this work in the highest terms to those who wish to increase their ability to interpret clinical electrocardiograms.

That he should agree wholly with every view expressed, or with the interpretation of all of the records reproduced, is hardly to be expected. Our knowledge of electrocardiography is not only far from complete; it is in rapid and vigorous growth. Under these circumstances a difference of opinion on many points is desirable and inescapable. Space is not available for detailed consideration of a number of electrocardiograms which, in the opinion of the writer, are wrongly interpreted, or show important features which are not mentioned in the text. In the way of general criticism the following comments are offered.

In the preface it is stated that clinical electrocardiography is an empirical science, and that it has developed by the careful study of records obtained in various types and stages of cardiovascular disease. This is emphatically not the case; if the knowledge gained from the very beginning, long before Einthoven to the present, by experiment, guided by well-conceived hypothesis, were taken away, there would be precious little left, either of the background or of the foreground of the subject.

The description and interpretation of each of the records reproduced is preceded by a brief but excellent summary of the relevant clinical data. The addition of this material is to be highly commended. It emphasizes the importance of considering the patient's history, the physical signs, and the laboratory data, including the electrocardiogram, together, instead of depending on any one of these alone. Unfortunately, however, Gruybiel and White do not always make clear to what extent the conclusions which appear at the end of their discussion are based mainly upon the clinical data, and to what extent these conclusions are based upon the electrocardiographic observations. This may have the unfortunate result of encouraging the inexperienced to read far more into the electrocardiogram than can possibly be justified. It is often possible to make the diagnosis of myocardial infarction from the electrocardiogram alone, and tracings taken during an attack of angina pectoris may show changes characteristic of transient myocardial ischemia, but apart from these conditions the reviewer does not believe that "coronary disease" produces any electrocardiographic abnormalities that can be considered characteristic. It would be better if this term were never used under any circumstances in connection with the interpretation of the electrocardiogram.

FRANK N. WILSON.

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To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is \$5.00 a year and journal membership at \$11.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

\**Executive Committee.*

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